SCIENTIFIC DISCUSSION

1 Introduction

ZOSTAVAX is a live attenuated vaccine. It is manufactured from the same virus strain and by the same process used to produce VARIVAX, a live varicellazoster virus (VZV) vaccine for prevention of chickenpox. The Drug substance (DS) is equivalent to that in the approved monovalent VZV vaccine, VARIVAX, and the VZV component in the tetravalent vaccine, ProQuad. However, ZOSTAVAX is manufactured at a higher virus titre than VARIVAX and ProQuad.

Infection with varicellazoster virus (VZV), an alpha herpesvirus, is associated with two distinct diseases; varicella and herpes zoster. Primary infection results in chickenpox (varicella) a generally mild, self-limiting illness usually acquired in childhood or adolescence and affecting almost all individuals. Following initial primary infection with VZV, the virus remains latent in the dorsal root ganglia. It is assumed that latent virus may frequently reactivate and replicate subclinically. These episodes of transient subclinical viremia lead to repeated antigenic stimulation of immunity without clinical manifestations of disease. In some individuals, however, reactivation and replication of the latent virus result in the clinical manifestation of herpes zoster (HZ), which is often referred to as shingles.

HZ is characterized by a unilateral, vesicular rash with a dermatomal distribution that generally corresponds to the area of skin innervated by a single spinal or cranial sensory ganglion. Typically, the vesicles crust over in 7 to 10 days, but may take up to a month to heal. One of the most significant clinical manifestations of HZ is pain, which is considered to be due to VZV induced neuronal destruction and inflammation. HZ-related pain may occur during 3 time periods:

- prior to onset of the cutaneous eruption (prodromal pain, typically beginning 3 to 5 days prior to the appearance of skin lesions):
- during the period of the acute rash (acute neuritis), and following healing of the acute skin lesions;
- beyond cutaneous healing for a prolonged period of time (postherpetic neuralgia, PHN).

PHN, the most severe sequelae of HZ, occurs in 10-20% of HZ patients and is described by characteristic patterns of pain with the majority of patients experiencing the following patterns

- constant pain described as burning, throbbing or aching pain;
- intermittent sharp, stabbing, shooting, lancinating pain;
- stimulus-evoked pain as allodynia that usually lasts well beyond the duration of the stimulus. Allodynia, which is present in at least 90% of PHN patients, is typically described as the most distressing and debilitating component of HZ

The mechanisms leading to HZ are not well understood, however, one predisposing factor in developing HZ in immunocompetent persons is advancing age. The incidence and severity of HZ increase from 2.5 per 1000 person-years in adults aged 20–50 years to 7.8 per 1000 person-years in those aged >60 years. Furthermore, complications such as PHN, which are relatively infrequent in otherwise healthy children and younger adults, occur in almost one-half of older individuals. It is postulated that the age-related increase in the risk of HZ among otherwise healthy elderly subjects is attributed to immunosenescence and has been correlated with a diminished cell-mediated immunity (CMI), but not with the level of circulating VZV specific serum antibodies. However, studies conducted in immunocompromised patients indicate, that low or absent CMI represents a necessary, but not a sufficient condition for the occurrence of HZ.

2 Quality aspects

Introduction

The finished product is presented as a powder and solvent for suspension for subcutaneous injection in a single 0.65 ml dose. The lyophilised powder is presented in a vial (Type 1 glass) with a butyl rubber stopper and flip-off aluminium seal. The finished product contains the following excipients: sucrose, hydrolysed porcine gelatin, sodium chloride, monosodium L-glutamate, anhydrous disodium phosphate, potassium dihydrogen phosphate, potassium chloride, and sodium hydroxide (pH adjustment).
Before use, each vial is to be reconstituted with water for injections supplied in either a vial (Type 1 glass) with a butyl rubber stopper or in a prefilled syringe (Type 1 glass) with plunger stopper and tip cap (chlorobutyl rubber).

The lyophilised vaccine must be stored frozen at -15ºC or colder, whereas the diluent should be stored refrigerated or at room temperature. Therefore, the product is shipped using a styrofoam box allowing packing the frozen component and the non-frozen component together. This polystyrene container is composed of two compartments. The frozen component is placed in the lower compartment where dry ice is used as the refrigerant. The non-frozen component is placed in the receptacle compartment in the lid, so it is not exposed to the freezing conditions of the dry ice.

After reconstitution, one dose (0.65 ml) contains:

Varicella-zoster virus[1] Oka/Merck strain (live, attenuated)..... not less than 19400 PFU*

* plaque-forming units

([1]) Produced in human diploid (MRC-5) cells.

Active substance

Seed lot system

The Oka strain of the varicella-zoster virus (VZV) was isolated from fluid taken from the vesicles of a 3-year-old boy with a case of chicken pox. The virus was isolated in primary human, embryonic lung cells (HEL) and was passaged 11 times. The strain was further passaged 12 times in guinea pig embryo fibroblasts (GPE) to attenuate the strain and once in human diploid cells (WI-38) to passage 24. One vial of frozen infected cells of the passage 24 Oka VZV strain was received by Merck on March 1984 from Osaka University. Although no clinical studies with ZOSTAVAX have been conducted using VZV from the passage levels intended for commercial production, varicella-zoster vaccine at the passage level for production was developed and evaluated in the setting of the applicant's monovalent varicella vaccine, VARIVAX. The preparation of master seed and stock seed lot are appropriately described in the dossier.

Human diploid fibroblast cells (MRC-5) as cell substrate

MRC-5 cells, a human, embryonic, lung, fibroblast cell line (diploid, male) originally isolated by J.P. Jacobs at the National Institute for Medical Research (London, England) and deposited at approximately population doubling level (PDL) 7 at the National Institute for Biologicals Standards and Controls (NIBSC).

Manufacture of varicella harvested virus fluids (HVFs)

A vial from the MWCB is thawed and planted into cell factories. Cells are trypsinized and finally planted into roller bottles for infection.

Based on appropriate criteria, the concentration of the working seed is adjusted. Each production roller bottle is planted with working cell suspension and incubated. The spent medium is removed and discarded, and each cell culture is rinsed. Stabilizer is added; the suspension is removed and stored with appropriates conditions. A batch of HVF represents mechanically harvested, VZV MRC-5 cells.

Manufacture of dispensed bulk

VZV dispensed bulk is a blend of HVF lots. The cells in the HVF suspension are disrupted and clarified. The dispensed final bulk containers (dispensed bulk) comprise a batch of the active substance and are stored frozen.

Control cell Cultures and Harvest Control Fluids (HCFs)

Final harvested control fluids are tested for sterility, mycoplasms, and tissue culture safety, while cells are tested for hemadsorption.

Controls of materials and critical steps / process validation

The MRC-5 MCB and WCB are tested to ensure freedom from extraneous agents and to ensure that the cells behave normally through production use PDL. Release testing is described at appropriate process steps and will be performed in compliance with Ph. Eur 5.2.3.
Release testing of the VZV master seed and stock seeds is performed in compliance with Ph. Eur. The applicant committed to consult the EMEA to discuss if test for monkey neurovirulence on any new VZV master seed is still required via the new Ph. Eur. Monograph on zoster vaccine.

Within each manufacturing process step, goals, critical process parameters (CPPs), and critical quality attributes (CQAs) were determined, along with appropriate specifications and acceptance criteria.

- ***Characterisation and specifications***

The complete sequence of the Oka/Merck strain and the wild-type Oka parent have been determined.

Process-related impurities arising from the VZV vaccine bulk manufacturing processes are classified as cell-substrate or cell-culture derived. Cell-substrate-derived impurities may include proteins derived from the host cell line; cell-culture-derived impurities may include antibiotics (e.g., neomycin), serum, or other media components. VZV process uses cell growth medium containing bovine calf serum. Serum protein clearance is provided by rinsing the cell layers to remove as much serum as possible prior to virus harvest. Each VZV final bulk is tested for BSA.

Assays are performed at several stages of processing of vaccine bulks in order to confirm absence of extraneous agents, to verify potency and identity, and to provide a measure of quality and process consistency. Assays involved in release testing of drug substance are performed according to approved control procedures that describe the main steps in a procedure. Most assays performed on VZV vaccine bulks and bulk intermediates are qualitative methods for which the experimental outcome is only: growth or no growth, absence or presence etc. In many of these cases, the assay specifications are compendial. For quantitative assays, the acceptance criterion is based on historical data.
The validation was performed using the assay procedure that was in place at the time the assays were validated. The parameters that were evaluated as part of the method validation for the assays were provided for each analytical procedure.
Batch analysis results have been provided for eleven batches of HVFs, and ten batches of dispensed bulk lots used in Zoster vaccine lots. Consistency of production was demonstrated and all lots met the pre-set specifications.

The reference material used for the VZV potency and antigen content is described appropriately. To generate an antigen reference standard lot, material from multiple VZV final bulk lots is pooled, filled, and lyophilized according to procedures applied in VARIVAX vaccine manufacture. Varicella antigen content in a new reference standard is established by calibration against a previously qualified

reference standard. The applicant has committed to revise the procedure used to calibrate the VZV reference standards.

- ***Stability***

Formal stability studies with the VZV final bulk were initiated for three lots Stability results for these three lots of VZV final bulk are available.

Finished product

ZOSTAVAX is a sterile lyophilized vaccine prepared by formulating the Oka/Merck strain of the attenuated live VZV. Sterile water for injections is provided for reconstitution. The product is intended for single-dose administration and contains no preservative.

- ***Pharmaceutical Development***

The formulation composition of ZOSTAVAX is based on the formulation compositions of the currently licensed frozen formulation of the monovalent VZV vaccine, except for the virus titre. Consequently the virus is known to be compatible with the stabiliser. The excipients and their concentration in the filled container prior to lyophilisation are equivalent and the lyophilization cycle for ZOSTAVAX is comparable, to that used for the monovalent VZV vaccine.

Several vaccine lots have been used in clinical trials with differences in the VZV titres and lot sizes. The manufacturing process for the DS changed in 1998, therefore DS batches from the so-called 1994-1995 process and 1998 process (current manufacturing process) have been used in the production of the lots used in clinical trials. The filling and lyophilisation is said to been carried out in a comparable way to the VARIVAX process. For all clinical protocols the target fill volume was 0.7 ml and the administered volume was 0.5 ml, except in study 009 where 0.7 ml or 1.0 ml was filled and 0.65 ml of the reconstituted vaccine was administered. For the study 004 the vaccine was aged in refrigerator to reduce the number of PFU to mimic the quality of the product at the end of the shelf-life.
In addition to clinical lots, lots for use in stability studies and manufacturing process validation studies have been produced with the current DS process. In 1998 three full-scale process validation DP batches were produced using the formulation and filling processes used at that time. In 2003 the formulation and filling processes were modified. Thereafter three pilot scale zoster vaccine batches were produced for stability studies. In addition, in 2004 three full-scale DP batches were produced to validate process and equipment improvements and pressure control during lyophilisation.

Each vial is reconstituted with the entire volume of the provided diluent and the entire volume of the reconstituted vaccine is administered to ensure a targeted 0.65 ml dose. Consequently there is no actual overage.

- ***Manufacture of the Product***

All manufacturing operations are performed at Merck & Co., Inc, West Point, Pennsylvania, USA.

The starting materials for zoster vaccine are PGS stabilizer and frozen dispensed bulk. Prior to thawing, the volume of each dispensed bulk to be added is determined by potency release testing of the final bulk. Immediately after thawing, the DS is blended with the PGS stabiliser solution in Class 100 conditions. The FFB is then sampled for sterility testing. CPPs are identified.

Automatic filling machines aseptically fill vials, and then the vials are lyophilized for an appropriate cycle time.

The vials are removed from the lyophilisation chamber and stored at appropriate temperature prior to sealing. The time that vaccine is held at room temperature during sealing, inspection, labelling, packaging, and assembly operations is documented. The maximum combined time at room temperature after lyophilisation for all operations is constrained to ≤12 hours. Inspected sealed vials

are stored at ≤-20°C (maximum 6 months) until they are packaged. After packaging, the vaccine may be stored at -15°C or colder for a maximum of 18 months as stated in the Summary of Product Characteristics. CPPs and CQAs of the filling process are identified and include filling mass, formulated bulk temperature, maximum time in solution of the active substances, transfer time to the lyophilisation cabinet and lyophilisation cycle pressure, time and temperature

Qualified insulated containers have been designed specifically for frozen vaccine shipments. During transport to Europe a temperature below –20 ºC is maintained.

Process validation for ZOSTAVAX was successfully performed by comparing the results of three validation lots. The validation results demonstrate that the predefined specifications for CPPs and CQAs were met.

Both, the sterile diluent in a syringe with fixed-needle and the diluent in a syringe without needle syringe are manufactured by an outside vendor. The diluent in a vial is manufactured by Merck & Co., Inc, West Point, Pennsylvania, USA.

At the outside vendor, Water for Injections (WFI), manufactured by distillation of purified water, is filled into glass syringes and sterilized. Raw materials are tested according to standard operating procedures or according to specifications and methods described in pharmacopoeias. Raw materials are in accordance with specifications. The manufacturing process is described in detail and all relevant information regarding quality control, validation of the manufacturing process and stability of the diluent have been provided by the applicant.

At Merck, WFI, manufactured by distillation of deionized water, is filled into glass vials and terminally sterilized. The manufacturing process is described in detail and all relevant information regarding quality control, validation of the manufacturing process and stability of the diluent have been provided by the applicant

- ***Control of excipients***

Except for hydrolyzed porcine gelatin the stabilizers used are compliant with all existing compendial monographs. Gelatin is the only excipient of animal origin, and is derived from non-ruminant sources and therefore in compliance with Ph. Eur. Chapter 5.2.8. Adventitious agent testing for hydrolyzed gelatin is performed at Merck.

- ***Product Specification***

The same tests are part of the release testing of VARIVAX and ProQuad batches.

Tests are performed on the drug product to ensure safety, sterility, to confirm the identity and quantify the potency of the product, and to provide a measure of process consistency. Assays employed in control of the finished product lots are performed according to approved Control Procedures (CPs) that describe the main steps in a procedure.

Each dose of the vaccine contains at the end of its shelf-life a minimum 19,400 plaque forming units (PFU) of VZV. The release specifications have been selected to ensure that, at expiry, each dose will contain the aforementioned minimum potency when the vaccine is reconstituted and stored at room temperature for 30 minutes.
Several assays performed on the finished product are qualitative methods for which there are only two experimental outcomes (growth or no growth, absence or presence, etc.). In many cases, the assay specifications are compendial.

The potency specifications for filled container have been derived from several sources. The VZV release potency is described in the dossier.

The parameters that were evaluated as part of the method validation for the assays are listed for each analytical procedure. When applicable, the assay parameters addressed were specificity, inter-assay precision, limit of detection, limit of quantisation, linearity, range, ruggedness, and robustness.

Batch analysis was performed on pivotal clinical study lots, stability study lots and three full scale process validation lots. All results met the pre-defined specifications.

Because ZOSTAVAX is a live virus vaccine that contains varicella-zoster vaccine bulk, with a viral component that is strongly associated with the cell membrane, it is not a highly purified product. To provide a marker for removal of residuals from the cell culture process, a quantitative test for residual BSA is conducted on the vaccine bulks used for filling. The BSA content in the final containers is a calculated value that is derived from the input volumes and the measured BSA concentration of the individual VZV bulks along with the input volume of PGS stabiliser. A specification exists for BSA content in filled container (≤500 ng BSA per single human dose) as per the Ph. Eur. monograph 0648 for the pediatric Varicella vaccine even though filled container material is not directly tested. Because of the relatively high virus titre required for this vaccine it has been agreed that the specification for residual BSA deviates from the one of the monograph (650 ng per dose or 1 μg/ml). The applicant has proposed the development of a new Ph. Eur. Monograph for zoster vaccine.

Two reference standards (house standards) have been used for potency assays of this product. . The Applicant has committed to monitor the stability of the standards.

- ***Viral safety and TSE***

Adventitious Agents

All raw materials used in vaccine manufacturing are tested for adventitious agents prior to release and use in manufacturing. Validated processing steps that add additional levels of confidence for the absence of adventitious agents are filter sterilization and ultraviolet (UV) - or gamma -irradiation.

TSE

The manufacturing process for ZOSTAVAX was evaluated for the theoretical risk of transmission of infectivity associated with BSE prions, with the conclusion that the risk of BSE transmission in ZOSTAVAX is exceedingly remote. The rationale and the calculation for the theoretical risk of transmission of infectivity associated with BSE prions were provided.
Biological reagents used in the manufacture of the vaccine bulks or bulk intermediates include iron-enriched bovine calf serum (BCS), fetal bovine serum (FBS), porcine pancreatic trypsin, gelatin (porcine-derived hydrolyzed), and amino acids. Certificates of Suitability (CoS), which are granted by the European Directorate for the Quality of Medicines (EDQM), and the measures applied (e.g. regular audits of vendor facilities, testing to ensure that the appropriate quality standards are met, etc.) ensure that the ruminant-derived raw materials currently used in manufacturing carry no TSE-related risk.

- ***Stability of the Product***

Stability tests have been designed to measure product performance under anticipated handling and storage conditions and under stressed conditions that might be encountered after distribution. The anticipated conditions following lyophilisation were studied. Upon use, the vaccine is reconstituted and may be stored for up to 30 minutes at room temperature prior to injection.

The stability studies were conducted on formal stability study lots at various temperatures described in the dossier suitable to support the storage conditions of the vaccine. The virus undergoes a statistically significant loss of potency when stored at 2-8 °C or higher, which underscores the importance of frozen storage of the vaccine.

The cumulative data from all stability studies performed indicate this vaccine to be satisfactorily stable for at least 18 months from the date of manufacture when stored at -15 °C or colder (frost-free). The agreed shelf-life of 18 months includes up to 12 hours at room temperature for sealing, inspection, and packaging, up to 6 months of storage at -20 °C prior to packaging and up to 30 minutes at room temperature following reconstitution immediately prior to use as stated in the SPC.

Stability studies on the formal stability lots are on-going. Stability studies on the validation lots has also been initiated. In addition, post-launch vaccine lots will be placed on stability on an annual basis for the purpose of routine monitoring. Full testing will be performed at initial and expiry intervals; a subset of the tests will be performed at each time interval as appropriate.

Discussion on chemical, pharmaceutical and biological aspects

During the evaluation of ZOSTAVAX, no major objections were identified. With regards to other concerns, the applicant was asked to revise the upper release specification according to reflect the process capability. An upper limit was argued by the applicant to be required to compensate for titre losses, associated with the intended up-scaling of the process and subsequent prolongation of manufacturing process. Since this may cause inconsistency within and between production batches, this approach was regarded not acceptable.
The revised upper specification per dose is based on estimated overall variability, known liquid degradation rate, and current validated batch size. In addition, an alert limit per dose on last tray of the lyophilisation process will trigger testing of first tray to ensure that the upper specification is not exceeded. The applicant also acknowledged the constraint to smaller batch sizes.
The applicant also indicated that this target final formulated bulk potency value may change as additional experience with the formulation, filling and lyophilisation processes is gained. Therefore, the applicant committed to re-evaluate the final formulated bulk target potency value when more experience on the lots and process is available.

Regarding the stability and calibration of varicella standards used for varicella potency assays, the issues are resolved, resulting in follow-up measures. The applicant committed to revise the procedure used for calibrating the varicella standard and to monitor the stability of the reference standards and report the results on a regular basis.

Several commitments are made by the Applicant, and several follow-up measures are defined to provide further information post-approval. In conclusion, all quality issues are resolved.

3 Non-clinical aspects

Introduction
No non-clinical data were submitted for ZOSTAVAX. The applicant, referring to the CHMP Note for guidance on Preclinical Pharmacological and Toxicological testing of vaccines (CHMP/SWP/465/95) argued such studies not to be relevant in view of the lack of relevant animal models and the long historical experience with varicella live viral vaccines. This position is endorsed.

The contra-indication for pregnancy is based on the clinical experience in clinical infection with the wild-type strain (occurrence of congenital varicella syndrome or other birth defects) but is is not known whether ZOSTAVAX can cause foetal harm when administered to a pregnant woman.

Pharmacology
Traditional pharmacodynamic studies have not been performed for ZOSTAVAX because of the lack of relevant animal models to study vaccine pharmacology. CPMP/SWP/465/95 guidance recognizes that suitable animal models are not always available and that standard pharmacological and toxicological testing may not be required for live virus vaccines, and such studies were not conducted previously for VARIVAX.

Pharmacokinetics
Absorption, distribution, metabolism, excretion, or conventional pharmacokinetic drug interactions of the active ingredients are not relevant for evaluation of live attenuated viral vaccines that induce the immune response as a consequence of virus replication.
There are no non-clinical pharmacokinetic drug interaction study reports. Drug interaction studies have not been performed because of the lack of relevant animal models to study viral vaccine antigen interactions.

Toxicology
Traditional toxicity studies have not been performed because of the lack of relevant animal models to study toxicology of viral vaccines antigens. CPMP/SWP/465/95 guidance recognizes that suitable animal models are not always available and that standard pharmacological and toxicological testing may not be required for live virus vaccines, and such studies were not conducted previously for VARIVAX. However, exhaustive safety testing was performed for the absence of transmissible or infective viral agents according to requirements listed in the European Pharmacopoeia, Supplement 2002, Section 2.6.16, “Tests for Extraneous Agents in Viral Vaccines for Human Use.”

Ecotoxicity/environmental risk assessment
It is anticipated that the environmental impact of zoster vaccine live would be very low for the following reasons:
- Minimal viral shedding has been associated with attenuated viruses
- Viral shedding in body fluids occurs at a much lower rate than that observed with wild viruses, and is not prolonged.
- Viruses are rapidly inactivated outside the human host.
- Excretion of vaccine virus has been rarely linked to disease transmission.
- There is no proven animal reservoir capable of sustaining transmission of VZV. Neither a carrier state nor a vector has been identified.

4 Clinical aspects

Introduction

The clinical development program of ZOSTAVAX consisted mainly in 8 protocols in which approximately 40,000 subjects were enrolled and vaccinated. An overview of main clinical trials performed to evaluate the efficacy, safety and immunogenicity is given in the table below.

Efficacy and safety of the zoster vaccine was studied in one pivotal randomized, double-blinded, placebo-controlled, multicenter study (protocol 004). In this study 38,546 subjects were enrolled and vaccinated. Out of them 19,270 received the zoster vaccine and 19,276 received placebo. In addition, two sub-studies were conducted to further evaluate adverse event and Cell Mediated Immunity (CMI). 6,616 subjects were enrolled in the Adverse Event Monitoring substudy and 1395 subjects were enrolled in the CMI substudy. The study was recently published (N Engl J Med 352:2271-84,2005).

Protocols 001 and 002 were dose-response studies, presenting both safety and immunogenicity data. Use of the zoster vaccine in populations with chronic diseases (such as chronic obstructive pulmonary disease and type II diabetes mellitus) was also evaluated in protocol 002. Safety and immunogenicity of zoster vaccine in VZV-seronegative adults were studied in protocol 003. Protocols 007, VARIVAX Protocol 049, and ProQuad Protocol 012 were safety and immunogenicity studies. Protocols 005 and 009 were safety studies.

Summary of clinical studies conducted to evaluate efficacy, safety and immunogenicity of ZOSTAVAX

Protocol Number	Study Title	Design	Dosage Potency per Dose	Study population	Primary Study Objectives
001 Phase I	Pilot Dose-Ranging Study to Assess the Safety and Tolerability of Live, Attenuated (Oka/Merck) Varicella-Zoster Vaccine in Healthy, Seropositive Adults 60 Years of Age and Older	Randomized, double-blind, placebo controlled study	1 dose s.c. 2,000 PFU 8,000 PFU 17,000 PFU 19,000 PFU 34,000 PFU 67,000 PFU Placebo	Total: 276 Age range: 60-92 years	Safety and tolerability profile of the 6 vaccine lots with varying potencies.
002 Phase IIb	Dose-Selection Study Using Live Attenuated (Oka/Merck) Varicella-Zoster Vaccine in Healthy Adults and in Adults With Diabetes Mellitus or Chronic Obstructive Pulmonary Disease 60 Years of Age and Older With a History of Varicella	For dose 1: randomized, double-blind, placebo controlled study For dose 2: Open-label	2 doses, s.c. 0, ~18 mos <u>Dose 1:</u> 34,000 PFU/dose 50,000 PFU/dose or Placebo <u>Dose 2:</u> All subjects received 50,000 PFU	Total: 398 Age range: 59-89 years	The primary objective for the first dose (Protocol 002-01) was to select a vaccine potency formulation that was safe and well tolerated. The primary objective for the second dose (Protocol 002-02) was to assess the safety of the vaccine as a second vaccination.
003	Probe Study to Evaluate the Safety and Tolerability of High-Potency, Reformulated, Live, Attenuated Oka/Merck Varicella-Zoster Vaccine in Healthy Adults 30 Years of Age and Older	Phase 2b, design as randomized, double-blind, placebo-controlled, study population should show 21 enrolled,	Dosage Potency 50,000 PFU	1148 (screened) Age range 27-69 years	(1) To investigate the safety and tolerability profile of a vaccine formulation in healthy subjects who have low VZV antibody titer (seropositive and 5 gpELISA units/mL) or undetectable VZV antibody (measured by gpELISA) 30 years of age and older.
004 Phase III	Trial of Varicella-Zoster Vaccine for the Prevention of Herpes Zoster and its Complications	Randomized, double-blind, placebo controlled study Subjects were expected to be followed for an average of 4.5 years. Two substudies: -AEM Substudy -CMI Substudy	1 dose, s.c. 19,000 to 60,000 PFU or Placebo	Total: 38,546 Age range: 59-99 years - 59 years: 1 - 60-69:years: 20,746 - ≥70 years 17,799 AEM substudy: Total: 6616 CMI Substudy:	<u>Co-primary objectives</u>: 1. To determine if immunization with zoster vaccine will reduce the incidence and/or severity of HZ and its complications, primarily PHN, in persons 60 years of age and older. 2. To determine if immunization with zoster vaccine will protect against PHN.

				Total: 1395	
005 Phase IIb	Probe Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Process Upgrade Varicella-Zoster Vaccine as a Booster Dose in Previously Vaccinated Adults 60 Years of Age and Older	Uncontrolled, open-label study	1 dose, s.c. 50,000 PFU	Total 196 61-89 years	Safety of PUVV given to subjects who have previously received 1 or 2 dose(s) of varicella vaccine.
007 Phase IIa	A Double-Blind, Placebo-Controlled, Randomized Study to Evaluate Safety, Tolerability, and Immunogenicity After 1 and 2 Doses of Zoster Vaccine	Randomized, double-blind, placebo controlled study	2 dose s.c. 0, 42 d 10,000-20,000 PFU	Total 209 58-90 years	To compare the VZV IFN-γELISPOT response ~6 weeks after 1 and 2 doses of zoster vaccine with the VZV IFN-γELISPOT response ~6 weeks after 1 and 2 doses of placebo.
009 Phase III	Evaluation of the Safety and Tolerability of a Higher Potency Dose of Varicella Zoster Virus Vaccine Live (Oka/Merck) Among Adults 50 Years of Age and Older	Randomized, double-blind, active-controlled study	1 dose s.c. 207,000 PFU 58,000 PFU	Total 695 50-90 years	To compare the safety and tolerability profile of a higher potency zoster vaccine with that of the zoster vaccine at a lower potency.
VARIVAX ™ 049	Multi-center, Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 2-Dose Regimen of High-Titered (~50,000 PFU/0.5mL) PUVV in Subjects ≥13 Years of Age	Randomized, double-blind	2 doses ~50,000 PFU/dose of PUVV 5400 PFU/dose of VARIVAX	Total 1366 13 – 69 years	(1) To determine if PUVV will yield a similar immune response as VARIVAX™ 6 weeks after the second dose. (2) To assess the safety and tolerability of PUVV after Doses 1 and 2.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

No pharmacokinetic studies were performed. As stated in Section 3.2.1 on the CHMP "Note for Guidance on Clinical Evaluation of New Vaccines" (CPMP/EWP/463/97 dated 19 May 1999), pharmacokinetic studies are generally not required for injectable vaccines because they do not provide information useful for establishing adequate dosing recommendations.

Pharmacodynamics

The pharmacodynamic principles of vaccines can be described as the induction of a qualitative and quantitative acceptable immune response within an acceptable time frame suitable to protect from infection with the wild-type antigen or in the case of the zoster vaccine to prevent clinical relapse of VZV infection leading to HZ. Successful achievement of an anamnestic immune response is controlled by measuring surrogate parameters present in the serum of vaccinees like antibody concentrations (=antibody titers) or cell mediated immune responses. Consequently, no conventional pharmacodynamic studies were performed.

Immunogenicity

Pharmacodynamic evaluations assessing humoral response to varicella-zoster virus (VZV), using a glycoprotein enzyme-linked immunosorbent assay (gpELISA) and cellular response, using several assays including a VZV IFN-γ enzyme-linked immunospot (ELISPOT) assay, to the virus were assessed in Phase II and III studies.

The main goal in the development of zoster vaccine was to boost the VZV- specific (cellular) immunity in order to prevent the reactivation of the varicella virus. The key immunologic endpoints for clinical studies conducted in the zoster vaccine development program were the GeometricMeanTitres (GMT, measured by gpELISA) at 6 weeks post-vaccination, geometric mean counts (GMCs) (measured by VZV IFN-γ ELISPOT assay) at 6 weeks post-vaccination, the ratio (fold difference) of the immune responses of the zoster vaccine and placebo groups at 6 weeks post-vaccination, and the geometric mean fold rise (GMFR) from baseline to 6 weeks post-vaccination for both assays.

Results are described below for each individual study and discussed in the section on discussion of clinical efficacy.

Clinical efficacy

- Dose response studies

In dose ranging study 001 and dose selection study 002 zoster vaccine lots of different potencies ranging from 2000 PFU/dose to 67,000 PFU/dose were evaluated with respect to the safety and tolerability profile.

Pilot Dose-Ranging **Study 001** assessed the immune response and tolerability of attenuated (Oka/Merck) Varicella-Zoster Vaccine in 276 healthy, seropositive adults 60 years of age and older by using several doses ranging from 2000 PFU to 67 000 PFU. The observed IFN-γ responses were numerically higher in subjects who received the 19,000 PFU, 34,000 PFU, and 67,000 PFU potencies, compared with the placebo group and the lower potency groups. The IFN-γ responses appeared to plateau among these 3 higher potency groups, as judged by the geometric mean fold rises (1.5, 1.9, 1.7, respectively) or by the percent of subjects with ≥4-fold rises (30.0%, 28.6%, 29.4%, respectively). There were no significant differences in tolerability between the selected doses.

Study 002 was a randomised, double-blind, placebo-controlled, multicenter study to select a zoster vaccine potency that was well tolerated, in 398 VZV-seropositive adults ≥60 years of age with or without chronic illnesses such as COPD or DM. In the first phase, the study subjects received either placebo or a single dose of either 34 0000 or 50 000 PFU. A second dose (50 000 PFU) was given at month 18. The purpose of the second dose was to confirm the safety and immunogenicity of a higher potency zoster vaccine in subjects who were previously vaccinated with a similar or lower potency zoster vaccine or placebo.

The primary endpoints for the evaluation of the VZV-specific immune response for the first dose were the IFN-γ ELISA titer, VZV antibody level and Responder cell frequency (RCF) value at Day 0 and 6 weeks post-vaccination.

The primary endpoints for the evaluation of the VZV immune response for the second dose were (1) IFN-γ production (measured by ELISPOT and RT-PCR, if sufficient sample) summarised by geometric mean counts (GMCs) and fold rises from pre-dose 2 to 6 weeks post-dose 2; and (2) Responder cell frequency (RCF) responses summarized by geometric mean values (GMVs) and geometric mean fold rises from pre-dose 2 to post-dose 2.

After the first dose, IFN-γ ELISA and the VZV-specific ELISA demonstrated higher responses in the active groups compared with placebo but no difference between themselves. The responses were

comparable in healthy individuals as compared to patients with chronic illnesses. The responses were higher in individuals who were seropositive at baseline as compared to seronegative individuals. The immunological studies after the second dose failed for technical reasons.

Both the first and the second dose of the high potency vaccine were well-tolerated in both healthy individuals and in patients with chronic illnesses.

Overall, studies 001 and 002 showed that a potency range of ~22,000 to ~63,000 PFU per single dose of zoster vaccine is generally well tolerated. Considering that the humoral and cellular immune responses evoked by the different vaccine lots (2000 to 67,000 PFU per dose) indicated only a moderate dose-response relationship, an end of expiry potency of 19,000 PFU per dose was selected for the pivotal study 004.

Immune response to the second vaccine dose

All together, 470 subjects received 2 doses of zoster vaccine. The interval between doses varied in each protocol (42 days in Protocol 007, ~18 months in Protocol 002, and several years in Protocol 005). These studies did not reveal a clear booster effect although a clear immune response to the second dose was demonstrated. The safety profile of the second dose was not different from the single dose regimen.

Study 007 was a randomized, controlled, double-blind (with in-house blinding procedures), multi-centre study comparing the safety, tolerability, and immunogenicity profiles of 1 and 2 doses of zoster vaccine with those of placebo when administered to healthy subjects ≥60 years of age. A second dose of HZ vaccine given at any time post dose 1, in principle, restores but not significantly exceeds cell-mediated immune responses observed after the first dose as measured by gpELISA. In contrast, another immunological parameter, the VZV IFN- γ shows numerically higher values after the second dose, which could suggest a booster-like response, although the sample size and confidence intervals make interpretation difficult (see below).

Zoster 2-dose safety and immunogenicity study 007 – Summary of VZV IFN- γ ELISPOT responses by time point and vaccination group for the kinetics subset (per-protocol-population)

		Zoster vaccine (N=19)		Placebo (N=20)	
Endpoint	**Time point**	**n**	**Observed Responses (95% CI)**	**N**	**Observed Responses (95% CI)**
GMC	Prevaccination	19	21.4(9.2;49.6)	20	32.5(13.4;79.1)
	1 week postdose 1	16	102.2(38.0;275.3)	20	30.0(13.4;67.0)
	2 weeks postdose 1	15	26.7(7.8;91.8)	16	28.7(14.1;58.8)
	4 weeks postdose 1	17	34.2(15.9;73.5)	17	30.8(14.1;67.1)
	6 weeks postdose 1	17	55.3(28.3;108.3)	17	36.3(17.8;74.2)
	1 week postdose 2	11	191.0(109.6;332.9)	14	48.2(26.3;88.5)
	2 weeks postdose 2	15	87.1(31.9;237.9)	17	41.4(24.6;69.6)
	4 weeks postdose 2	14	65.3(19.4;219.2)	18	36.4(20.1;65.7)
	6 weeks postdose 2	8	100.3(37.1;270.9)	18	34.0(15.6;74.0)
	6 months postdose 2	13	75.0(43.5;129.3)	17	46.9(23.2;95.1)
Geometric mean fold rises from pre-vaccination	1 week postdose 1	16	4.0(1.2;13.8)	20	0.9(0.4;2.1)
	2 weeks postdose 1	15	1.0(0.3;2.9)	16	0.7(0.3;1.4)
	4 weeks postdose 1	17	1.4(0.4;5.0)	17	1.0(0.4;2.3)
	6 weeks postdose 1	17	2.1(0.7;6.0)	17	1.2(0.6;2.5)
	1 week postdose 2	11	5.7(1.6;19.7)	14	1.5(0.4;5.0)
	2 weeks postdose 2	15	3.1(0.9;10.6)	17	1.3(0.4;3.9)
	4 weeks postdose 2	14	2.2(0.5;10.0)	18	1.1(0.4;2.8)
	6 weeks postdose 2	8	3.7(0.5;28.5)	18	1.0(0.4;2.8)
	6 months postdose 2	13	2.4(0.9;6.5)	17	1.1(0.4;2.6)

N = Number of subjects vaccinated at baseline (Day 0) in each vaccination group.
n = Number of subjects who had valid VZV IFN-γ ELISPOT assay results at the respective time points in each vaccination group, or had valid results at both prevaccination and the respective postvaccination time point in the calculations of fold rise.

CI = Confidence interval;
GMC = Geometric mean count, in spot-forming cells per 10^6 peripheral blood mononuclear cells;
IFN- γ ELISPOT = Interferon-gamma enzyme-linked immunospot;
VZV = Varicella-zoster virus.

- Main study

STUDY 004 - Trial of Varicella-Zoster Vaccine for the Prevention of Herpes Zoster and its Complications – was the pivotal clinical study.

Methods

It was a randomised, double-blind, placebo-controlled, multicenter study (22 sites in the United States) to determine whether vaccination of older adults with zoster vaccine could decrease the incidence and/or severity of HZ and its complications, in particular, PHN.

The safety follow-up lasted through Day 42 post vaccination and subjects were expected to be followed for an average of 4.5 years.

Two substudies were performed:
- the Adverse Event Monitoring Substudy was designed to provide a detailed safety assessment of a subset of the main subject population,
- and the Cell-Mediated Immunity Substudy was designed to assess the VZV-specific immune responses of the vaccine recipients and to evaluate potential CMI correlates of protection against HZ and PHN.

Study Participants

The main inclusion criteria were:
- History of varicella or long-term (≥30 years) residence in the continental USA;
- 60 years of age or older.

The main exclusion criteria were:
- Immunosuppression resulting from disease, corticosteroids, or other immunosuppressive/cytotoxic therapy;
- Active neoplastic disease (except local skin cancer or other malignancies [e.g., prostate cancer] that was stable in the absence of immunosuppressive/cytotoxic therapy);
- Prior HZ;
- Prior receipt of varicella vaccine;
- Allergic sensitivity to neomycin;
- History of anaphylactoid reaction to gelatin;
- Significant underlying illness that would be expected to prevent completion of the study.

Treatments

Subjects received a single dose of zoster vaccine or placebo at Day 0. Subjects received a single 0.5-ml subcutaneous injection in the deltoid area of the nondominant arm. The estimated potency at vaccination of the 12 vaccine lots used in the study ranged from 18,700 to 60,000 PFU per dose. The median estimated potency of the zoster vaccine at vaccination was 24,600 PFU and more than 90% of vaccinated subjects received doses lower than 32,300 PFU. The zoster vaccine and the placebo contained the same stabilizers, but only the zoster vaccine included trace quantities of neomycin.

Antiviral therapy, famciclovir (500 mg every 8 hours for 7 days), was offered for treatment of HZ if the subject was seen within the 72 hours of onset of rash. If the subject was first seen beyond 72 hours of rash onset, famciclovir could be offered at the physician's discretion

Outcomes/endpoints

The study objectives were to determine whether vaccination of older adults with zoster vaccine could decrease the incidence and/or severity of HZ and its complications, in particular, PHN.

Initially, HZ pain Burden of Illness (BOI) was listed as the primary efficacy endpoint. However, incidence of PHN was treated as a co-primary endpoint for the efficacy analyses.

The HZ pain burden of illness (BOI) score was a composite endpoint incorporating the incidence, severity and duration of HZ pain. For each confirmed case of HZ, the ZBPI (Zoster Brief Pain Inventory) data were used to calculate a "HZ Severity of Illness Score", defined as the area under the ZBPI worst pain response-versus-time curve during this 182-day period (i.e., the HZ pain and discomfort severity-by-duration area-under-the-curve [AUC]). The HZ Severity of Illness Score was defined as zero for subjects who did not develop a confirmed case of HZ during the study and for 6 cases (2 vaccine recipients and 4 placebo recipients) with no pain assessments. The HZ BOI Score represented the average severity of illness among all subjects in the vaccine and placebo groups; it was calculated as the sum of the HZ Severity of Illness Scores of all members of a group divided by the total number of subjects (**N**) in that group.

PHN was defined by the presence of a typical rash and HZ-associated pain or discomfort, rated as 3 or greater (on a scale ranging from 0 to 10) and persisting or appearing more than 90 days after rash onset.

The diagnosis of HZ was confirmed by expert adjudication and viral testing.
Secondary endpoints were:
- incidence of HZ;
- duration of HZ pain;
- Activities of daily living interference due to HZ (ADLI).

Immune response *(tertiary objective)*:
The immune responses to the zoster vaccine were tested in the CMI Substudy at baseline and at six weeks, at 12, 24, and 36 months post-vaccination by using VZV interferon-gamma (IFN-γ) enzyme linked immunospot (ELISPOT) assay, VZV responder cell frequency (RCF) assay, and glycoprotein enzyme-linked immunosorbent assay (gpELISA). Exploratory analyses were also performed to determine whether the VZV-specific immune responses correlated with protection against HZ.

Sample size

Estimates made at the time the trial was designed indicated that a total of 400 confirmed cases of HZ and a total of 62 cases of PHN would be required. With a total enrollment of ~37,200 subjects (~18,600 per vaccination group), it was expected that the required cases of HZ and PHN would accumulate during an average of 4.5 years of follow-up, assuming an annual HZ incidence of 3/1000 in placebo subjects, and a conservative estimate of 10% annual loss to follow-up. A mean AUC for worst pain among cases of HZ in the placebo group was assumed to be 280, with a standard deviation of 212.

Based on a planned sample size re-estimation based on the first 200 evaluable cases of HZ, it was shown that that the mean variability of the HZ pain AUC scores for the first 223 evaluable HZ cases was greater than had been assumed for sample size calculations when the protocol was written. As a consequence, the number of evaluable HZ cases needed for the final analysis was calculated to be 750, an increase from the 400 cases specified in the original protocol, in order to maintain 97% power to detect a 60% reduction in burden of illness of HZ needed for the final analysis.
No sample size calculation was performed on the immunogenicity and safety endpoints, due to their exploratory nature.

Randomisation

Subjects were randomised in a 1:1 ratio to receive either zoster vaccine or placebo. The randomisation was stratified for two age groups (60 to 69 years, and ≥ 70 years).

Blinding (masking)

Because the placebo and the vaccine were visually distinct, an independent third party (vaccine technician) was responsible for labeling syringes and reconstituting and administering the vaccine/placebo. The unblinded vaccine technician had no subsequent role in the assessment of subjects and did not maintain any separate record of study vaccine or placebo assignments.

Statistical methods

The vaccine efficacy for the HZ BOI, VE_{BOI}, was defined as the relative reduction in HZ BOI Score in the zoster vaccine group compared with the placebo group and was estimated by:

$$VE_{BOI} = 1 - T_V / T_P,$$

where T_V and T_P are the estimated HZ BOI Scores for the zoster vaccine and placebo group, respectively.

The primary analysis was made using a modified-intention-to-treat (MITT) approach, which included all subjects who did not develop evaluable HZ within 30 days post-vaccination or who dropped out by day 30. Point estimate and confidence interval for VE_{BOI} were determined using special statistical methodology developed for this type of endpoint (Chang MN, Guess HA, and JF Heyse: Reduction in burden of illness: a new efficacy measure for prevention trials. Stat Med 1994; 13:1807-1814). The analysis was stratified by age group.

The vaccine efficacy for PHN, VE_{PHN}, was defined as the relative reduction in PHN incidence rate in the vaccine group compared with the placebo group and was estimated by:

$$VE_{PHN} = 1 - \lambda_V / \lambda_P,$$

where λ_V and λ_P are the incidence rates (person time data) of PHN in the zoster vaccine and placebo group, respectively.

The point estimate for VE_{PHN} and the associated exact 95% CI were determined by using Mantel-Haenszel type of methodology. The primary analysis was made for the MITT-population, and was stratified by the age group.

The vaccine efficacy for HZ, VE_{HZ}, was defined as the relative reduction of the HZ incidence rate in the zoster vaccine group compared with the placebo group.

In order to control the overall p-value among multiple tests of primary and secondary efficacy endpoints, Hochberg's stepwise procedure was used.

RESULTS

Participant flow

The patient disposition is seen in the table below. The number of discontinuations was small and evenly distributed among the treatment arms.

Subject Accounting for Subjects in the Main Study (004)

	Zoster Vaccine (N=19270)		Placebo (N=19276)		Total (N=38546)	
	n	(%)	n	(%)	n	(%)
Vaccinated:	19270	(100)	19276	(100)	38546	(100)
Completed:	18359	(95.3)	18357	(95.2)	36716	(95.3)
Discontinued:	911	(4.7)	919	(4.8)	1830	(4.7)
Died	793	(4.1)	792	(4.1)	1585	(4.1)
Withdrawn from the study	57	(0.3)	75	(0.4)	132	(0.3)
Lost to follow-up	53	(0.3)	40	(0.2)	93	(0.2)
Other	8	(0.0)	12	(0.1)	20	(0.1)

Completion data for the CMI substudy is also summarised below.

Subject Accounting for Subjects in the CMI Substudy

	Zoster Vaccine (N=691)		Placebo (N=704)		Total (N=1395)	
	n	(%)	n	(%)	n	(%)
Vaccinated:	691	(100)	704	(100)	1395	(100)
Completed:	676	(97.8)	681	(96.7)	1357	(97.3)
Discontinued:	15	(2.2)	23	(3.3)	38	(2.7)

Recruitment

The study was initiated on 06-Nov-1998, and the final HZ case was accrued on 30-Sept-2003. Last patient out was 28-Apr-2004 (with the exception of one subject who was contacted late). The cut-off date for in-house data was 23-Nov-2004.

Conduct of the study

Each subject was followed for the development of HZ for approximately 2 to 4.5 years. Subjects were instructed to contact study site personnel immediately if signs or symptoms of HZ occurred. An automated telephone response system (ATRS) was used to actively follow subjects on a monthly basis and inquire if any unreported potential HZ cases occurred during the previous month. During enrollment, each subject was educated on the signs and symptoms of HZ and the use of the ATRS. All suspected cases of HZ were to be clinically evaluated by a study site investigator within 24 hours of the first reported symptom.

Baseline data

The two vaccination groups were comparable with respect to the baseline characteristics (including gender, age, race, marital status, education, working status and health status).

Overall the study 004 included more male (59%) than female participants (22760 vs 15786, respectively). The median age in both groups was 69 years. 59% of the subjects were 60-69 years and 41% were≥70years of age. 6.6 % of the vaccine recipients and 6.9 % of the placebo recipients were 80 years of age or older.

Numbers analysed

The primary analysis was based on a modified-intention-to-treat (MITT) approach, which included all subjects who did not develop evaluable HZ within 30 days post-vaccination. Sixteen and 29 patients were excluded from MITT in the active and the placebo group, respectively. Three individuals had a second episode of HZ. In these cases, only the first episode was included in the analysis.

Outcomes and estimation

IMMUNOGENICITY OUTCOMES

Vaccine-associated immune responses pre- and postavaccination in VZV seropositive or seronegative adults.

Individuals in the target population for zoster vaccine generally have high baseline VZV antibody titers in the gpELISA. Nonetheless, following a dose of zoster vaccine, significant increases from baseline were seen at 2 and 6 weeks postvaccination, indicating that the vaccine elicits an anamnestic response. Among subjects enrolled in the CMI Substudy, the estimated Geometric mean titer (GMTs) at 6 weeks postvaccination were 478.7 gpELISA units/mL (mean fold rises from baseline (GMFR): 1.7) in the zoster vaccine group and 287.8 gpELISA units/mL (GMFR from baseline, 1.0) in the placebo group. The estimated fold differences for both GMT and GMFR between the zoster vaccine group and placebo group were 1.7 (95% CI = [1.6, 1.8]).

Regarding VZV IFN-γ ELISPOT Counts, the 6-week postvaccination response in the zoster vaccine group was significantly higher than in the placebo group, in terms of the Geometric mean count (GMC) (69.8 spot-forming cells [SFC]/106 PBMC in zoster vaccine group, 31.8 SFC/10^6 PBMC in placebo group) and the GMFR from Day 0 (2.1 zoster vaccine group, 0.9 placebo group). The estimated fold differences for both GMC and GMFR between the zoster vaccine group and the placebo group were 2.2 (95% CI = [1.9, 2.5]).

Persistence of VZV Antibody Titers by gpELISA Among the CMI Substudy Participants is summarised below.

		Zoster Vaccine (N=691)			Placebo (N=704)		
Endpoint	Time Point	n	Observed Responses	95% CI	n	Observed Responses	95% CI
GMT	Day 0	678	278.8	(258.0, 301.4)	691	291.0	(269.7, 314.0)
	6 Weeks	667	474.7	(441.5, 510.5)	684	291.4	(269.3, 315.3)
	12 Months	649	353.7	(328.1, 381.2)	661	306.6	(283.3, 331.9)
	24 Months	636	329.5	(304.5, 356.5)	644	300.6	(277.8, 325.3)
	36 Months	625	331.6	(305.1, 360.4)	612	305.7	(280.6, 333.2)
Geometric Mean Fold Rises From Day 0	6 Weeks	655	1.7	(1.6, 1.8)	673	1.0	(1.0, 1.0)
	12 Months	636	1.3	(1.2, 1.3)	650	1.1	(1.0, 1.1)
	24 Months	624	1.2	(1.1, 1.2)	633	1.1	(1.0, 1.1)
	36 Months	612	1.2	(1.1, 1.3)	601	1.0	(1.0, 1.1)

N = Number of subjects vaccinated in the CMI Substudy.
n = Number of subjects contributing to the immunogenicity analysis.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
CMI = Cell mediated immunity.
GMT = Geometric mean titer.
CI = Confidence interval.

In order to evaluate whether the vaccine-induced, VZV-specific immune responses correlated with protection against HZ, the responses by VZV IFN-γ ELISPOT assay and gpELISA were analyzed according to HZ status. This analysis was somewhat limited because the sub-study represented only 3.6% of the total study population, and relatively few substudy participants developed HZ during the

study. Furthermore, correlation between immune responses and protection against HZ were observed with gpELISA measurements, while, the results of VZV IFN-γ ELISPOT test had a less clear correlation to the protection.

VACCINE EFFICACY OUTCOMES

BOI related to HZ pain: The estimated VE_{BOI} was 61.1% (95% CI [51.1%, 69.1]).
The test of treatment-by-age-group interaction on BOI was not statistically significant (p=0.266).

Statistical Analysis of HZ BOI Efficacy Based on the Protocol-Defined AUC Scale Over 6 Months of Follow-Up After HZ Rash Onset (MITT Population) and adjusted for age and gender

	Zoster Vaccine (N = 19270)				Placebo (N = 19276)				Vaccine efficacy for HZ Pain BOI Point Estimate (95% CI)
	n	m	Total follow-up time (Person-Years)	Estimated HZ Pain BOI (Per 1000 Person-Years)	n	m	Total follow-up time (Person-Years)	Estimated HZ Pain BOI (Per 1000 Person-Years)	
All									
	315	19254	58203	2.208	642	19247	57736	5.682	0.611 (0.511, 0.691)
By Age Group (Years)									
60 to 69	122	10370	31323	1.495	334	10356	30953	4.334	0.655 (0.515, 0.755)
≥70	193	8884	26881	3.471	308	8891	26783	7.781	0.554 (0.399, 0.669)
p-Value for testing the vaccine efficacy for BOI >25% was <0.001; p-value for testing the vaccine efficacy for BOI >0% was <0.001; p-value for testing treatment-by-age-groupinteraction in vaccine efficacy for BOI was 0.266 . N = Number of subjects randomized. n = Number of evaluable HZ cases in the MITT population. m = Number of subjects in the MITT population. AUC = Area under the curve. HZ = Herpes zoster. BOI = Burden of illness. questionnaire MITT = Modified intention-to-treat. CI = Confidence interval.									

Incidence of PHN: The estimated VE_{PHN} was 66.5% (95% CI = [47.5%, 79.2%]).
The test of treatment-by-age-group interaction on PHN was not statistically significant (p >0.999).

Statistical al Analysis of the Incidence of PHN (MITT Population)

Zoster Vaccine (N = 19270)				Placebo (N = 19276)				Vaccine Efficacy with respect to PHN
n	m	Total Follow-Up Time (Person-Years)	Rate of PHN (Per 1000 Person-Years)	n	m	Total Follow-Up Time (Person-years)	Rate of PHN (Per 1000 Person-Years)	Point Estimate (95% CI)
27	19254	58203	0.464	80	19247	57736	1.384	0.665 (0.475, 0.792)
p-Value for testing the vaccine efficacy for PHN >25% was <0.001								

Incidence of HZ: The estimated VE_{HZ} was 51.3% (95% CI = [44.2%, 57.6%]). The test of treatment-by-age-group interaction on HZ was statistically significant (p-value<0.001). The reduction of HZ incidence was 63.9% (95% CI = [55.5%, 70.9%]) in the younger age (60 to 69 years of age) group and 37.6% (95% CI = [25.0%, 48.1%]) in the older age (≥70 years of age) group.

Incidence of Evaluable HZ Cases (MITT Population)

Age Group (Years)	Zoster Vaccine (N = 19270)					Placebo (N = 19276)				
	n	m	Total Follow-Up Time (Person-Years)	Observed Incidence Rate of HZ (Per 1000 Person-Years)	95% CI	n	m	Total Follow-Up Time (Person-Years)	Observed Incidence Rate of HZ (Per 1000 Person-Years)	95% CI
60 to 69	122	10370	31323	3.895	(3.2, 4.6)	334	10356	30953	10.791	(9.6, 12.0)
≥70	193	8884	26881	7.180	(6.2, 8.3)	308	8891	26783	11.500	(10.2, 12.8)
All	**315**	**19254**	**58203**	**5.412**	**(4.8, 6.0)**	**642**	**19247**	**57736**	**11.120**	**(10.2, 12.0)**

Compared with placebo, zoster vaccine reduced the duration of clinically significant pain (defined as the number of days between the first day after rash onset when the subject had a worst pain score ≥3 and the first visit when the worst pain score became <3 and remained <3 for the remainder of the follow-up period, up to 6 months following HZ rash onset) associated with HZ (median duration of clinically significant pain among HZ cases in the zoster vaccine and placebo groups: 20 days vs. 22 days; p-value<0.001 from the analysis based on the MITT population; p-value=0.041 from the analysis based on the evaluable HZ cases only). See below ancillary analyses with regard to reduction of HZ pain.

Compared with placebo, zoster vaccine resulted in an 8.2% reduction in the risk of having substantial ADLI (defined as having a combined ADLI score ≥2 for ≥7 days) beyond the reduction in HZ. The hypothesis testing on this endpoint was not statistically significant (p-value=0.341).

Ancillary analyses

Risk of developing PHN after HZ:

In terms of PHN incidence, there is a VE_{PHN} of 66.5 % throughout all study subjects. Referring only to subjects, developing HZ, there is a slight decrease in the risk of subsequently acquiring also PHN. In the vaccine group, the risk of suffering from PHN after HZ was 8.6 % (315/ 27), while in the placebo group it was 12.5 % (642/ 80). This effect was more prominent in the group of older subjects. The risk of developing a PHN after HZ (≥70 years old) was reduced to 9.8% among vaccinated subjects, compared to 18.5% for unvaccinated subjects with HZ.

Reduction of HZ pain

Among all subjects, who developed HZ, HZ pain Severity-by-Duration (0-6 month), a key component of the HZ BOI, was reduced by 21.8% in the vaccine compared to the placebo group (142.2 vs 180.5, p-value = 0.008).

With regard to the acute pain (pain between 0-30 days) there was no statistically significant difference between the vaccination group and the placebo group with regard to the Severity-by-Duration score, the mean score was 89,3 (95% CI 81.7, 96.8) and 91,8 (95% CI 86.6, 97.0) for the vaccine group and placebo group, respectively.

Following vaccination, the duration of clinically significant pain (3) associated with HZ in both age groups was significantly reduced (20 days vs 22 days, p-value < 0.001). However, less significant pain (<3) a reduction was observed only in the younger age group (30 vs. 36 days), while for the group of older participants no difference was found compared to the placebo group (<3; median duration 41 days for both groups).

The overall use of analgesic medication was similar in both study groups.

- Analysis performed across trials (pooled analyses and meta-analysis)

None

- Clinical studies in special populations

None

- Discussion on clinical efficacy

The main goal in the development of zoster vaccine was to boost the VZV- specific (cellular) immunity in order to prevent the reactivation of the VZV.

Cell mediated immune responses towards zoster vaccine were independent from the used dose (potency in terms of pfu/ml) of the vaccine virus and also from some other parameters known to be relevant for the immunogenicity and efficacy of vaccines, such as gender, co-morbidity and co-medication. In contrast, dependency was observed with regard to the age of individuals and possibly the number of doses administered (1 or 2).

Overall, in seropositive vaccinees, the zoster vaccine elicits significantly higher VZV specific responses compared to placebo as measured by gpELISA and VZV IFN-γ ELISPOT. Immune responses were shown to persist above baseline up to 36 months. However, the values decrease over time during the follow-up, being only slightly above baseline values at the end of the follow up. A dose of zoster vaccine, either 42 days or several years following initial VZV vaccination, elicits a VZV-specific immune response of a magnitude that is similar to that seen after an initial vaccination. Therefore, the persistence of immunity and protection against HZ was questioned for the long-term as well as after one dose as compared to two-dose immunization (with consideration to age categories).

The company agreed that there is a need to determine long-term duration of vaccine protection and committed to further assess the long-term efficacy through extension of follow-up of around 7000 vaccinated subjects (from study 004) for up to 10 years post vaccination, in order to detect potential waning of protection.

A second dose of HZ vaccine given at any time post dose 1 restores but not significantly exceeds cell-mediated immune responses observed after the first dose as measured by gpELISA. In contrast, another immunological parameter, the VZV IFN- γ ELISPOT may be increased significantly after a second vaccine dose. Although it is not possible for the time being to correlate any clinical benefit with cell-mediated immune parameters measured, this observation suggests that ZOSTAVAX individually stimulates different compartments of the human cellular immune system. To what extent individual and combined immunological effects do mutually contribute to vaccine efficacy cannot be explained for the time being.

Therefore, to date, without clear established correlation between an immune response and protection against HZ, there is no immunologic evidence that a 2-dose regimen would be superior to a single dose. A 2-dose versus 1-dose comparative efficacy trial would be difficult to perform because of the very large number of subjects to be included and no defined optimal dosing interval yet. Apart from further assessing the long-term efficacy of 1-dose regimen, the applicant proposed to consider studying immunogenicity.

The possibility of future changes in the epidemiology of HZ or PHN following introduction of ZOSTAVAX was discussed (e.g. delaying age of incidence of HZ or PHN) but there is currently no data to suggest such a change.

Clinical data demonstrate the efficacy of ZOSTAVAX in immunocompetent persons over 60 years of age, resulting in a decreased incidence and severity of HZ and its complications.

Overall, the vaccine reduced the incidence of HZ in the study population by 51 % and the incidence of PHN by 67%. An effect of the vaccine was observed with respect to the HZ"Burden of illness", which , besides the incidence of HZ, includes duration and severity of pain as an indicator of vaccine efficacy. Overall the vaccine efficacy for the HZ BOI was 61 %. There is currently no plausible explanation for, why the vaccine is not efficacious in preventing HZ in the remaining 49% of the vaccinees.

However, efficacy shows important differences with respect to the age of the vaccinee. The VE_{HZ} was about 64 % in the group 60 to 69 years of age, but only about 37 % in subjects ≥ 70 years of age. With respect to HZ BOI, the effect was also more pronounced in the younger age group (66.6% vs 56.4%), but this was not statistically significant. Though this effect is not fully understood, it seems to indicate that vaccination may be more effective at younger ages.

The applicant claimed the inclusion of the age group 50-59 years of age because the annual risk of HZ begins to increase markedly around 50 years of age. The incidence increases from approximately 2.5 per 1000 person-years in 40 to 49 year olds to approximately 5.0 per 1000 in 50 to 59 year olds and approximately 7.0 per 1000 in 60 to 69 year olds. Nevertheless, the pivotal study included subject of 60 years of age or older and therefore the number of vaccine recipients in the 50-59 years of age group is too limited to warrant this indication, even in view of some preliminary safety and immunogenicity data from additional subjects in a new study (Protocol 010) comparing two formulations of ZOSTAVAX including subjects 50 to 59 years of age (n = 135). Furthermore, it cannot be excluded that vaccination of individuals at the age of 50-60 years of age may postpone HZ to the older age groups where the disease is more severe.

Among subjects who develop HZ, there is a slight decrease in the risk of subsequently developing PHN, in the vaccine group compared to the placebo group, with a more prominent effect in older subjects.

Regarding the reduction of zoster associated pain, there was a statistical difference in duration and severity of pain between the two study groups. Regarding chronic pain, there was a significant reduction of severity-by-duration of HZ pain (22%) and a reduction of clinically significant pain (by two days). On the other hand, among subjects with HZ the relative reduction (of 31%) in interferences of Activities of Daily Living was not statistically significant and vaccination did not reduce the severity-by-duration of acute pain. Furthermore, the overall use of analgesic medication was similar in both study groups and there was no reduction in the rate of hospitalisation. Therefore, considering the correlation between zoster associated pain and HZ and PHN, a separate indication was not considered warranted, even if it was acknowledge that pain efficacy data could be described in the pharmacodynamic section of the SPC.

Persons with immunosuppressive therapies and individuals with primary or other immune disorders, as well as neurological disorders, multiple sclerosis and herpes simplex virus infections were excluded from the main efficacy study. The exclusion of these subjects was not related to safety concerns, but to the potential for these concomitant conditions to confound the evaluation of vaccine efficacy. Since no clinical data are available, vaccination in subjects with immunodeficency states, immunosuppressive therapy and active untreated tuberculosis is contraindicated and a warning on the lack of data in adults known to be infected with HIV is included in the SPC. The applicant also committed to study the safety and immunogenicity in some of the patient populations which were excluded from the pivotal study including mild and moderately immunocompromised, HIV-infected individuals or patients receiving chronic doses of systemic corticosteroid therapy.

Also because of the lack of data, the applicant committed to evaluate the safety, tolerability and immunogenicity of ZOSTAVAX in subjects who reported having experienced a previous episode of HZ.

Clinical safety

The safety of zoster vaccine was assessed in 6 randomised, controlled clinical studies (Protocols 001, 002, 003, 004, 007, and P009) and 1 open-label booster clinical study (Protocol 005). Five of these clinical studies were placebo-controlled. These studies were conducted between 1996 and 2004. Additional safety data on VARIVAX Protocol 049 was also submitted.

In each of the clinical studies safety was evaluated for 42 days after each injection of zoster vaccine, PUVV (high-titre VARIVAX), or placebo. Subjects were instructed to report all adverse experiences (AE) that occurred during the first 42 days post vaccination. Beyond 42 days post vaccination, all deaths and vaccine-related SAEs were also collected.

Different database technologies and adverse experience dictionaries (e.g. Costart, MedDRA) were used. Formal integration of all data was not feasible due to the different databases and dictionaries used across the studies.

- Patient exposure

The largest safety database is from Protocol 004, in which 38,546 subjects were enrolled (19,270 subjects received zoster vaccine). In this study a subset of 6616 subjects (3,345 subjects received zoster vaccine) across all study sites were enrolled in an Adverse Event Monitoring Substudy, which provided a more detailed evaluation of the vaccine's safety profile.

Protocols 001, 002, 004, 005, and 007 enrolled subjects who were ≥60 years of age. Protocol 009 enrolled subjects who were ≥50 years of age (n=185 subjects were between 50 to 59 years old). A total of 20,697 subjects who were vaccinated with at least one dose of zoster vaccine (20,456 of whom received the final vaccine formulation that will be used for marketing) were ≥50 years of age.

A total 144 subjects were 30 to 49 years. Protocol 003 enrolled subjects in tropical countries who were ≥30 years of age, although the numbers are small and therefore the results have limited impact. VARIVAX Protocol 049 targeted varicella history-negative subjects ≥13 years of age; the study population included both VZV- seropositive and VZV-seronegative subjects, with a small minority being ≥ 30 years of age.

598 subjects received a second dose of zoster vaccine or high-titered PUVV. Among those receiving a second dose, 481 subjects were ≥50 years of age and 117 subjects were 30 to 49 years of age.

The mean age of enrolled subjects for zoster vaccine evaluation was close to 69 years. The study population was predominately white.

The studies enrolled immunocompetent individuals, many of whom had concurrent, medically-stable chronic medical conditions that were typical of persons in the age groups studied. The most frequently reported prior medical conditions (incidence ≥20% in one or more vaccination group) were hypertension and arthritis.

- Adverse events

Protocol 004

In the routine safety monitoring cohort (Days 0 to 42 post vaccination) including all subjects, the percentage of subjects with one or more systemic adverse events was 8.3 % in the zoster group and 8.7 % in the placebo group. The AEs were comparable in both groups.

In the Substudy, 58.0% of the subjects in the zoster vaccine group and 34.4% of the subjects in the placebo group reported one or more adverse experiences (Day 0 through Day 42 post vaccination). This difference is accounted for in large part by the frequency of injection-site AEs (48.2 % in the zoster vaccine group and 16.6% in the placebo group). The most frequently reported injections site AE were erythema (35.7 % of subjects in the zoster group vs.7.0 % in the placebo group), pain/tenderness (34.5 % in the zoster group vs. 8.6 % in the placebo group), swelling (26.2 % in the zoster group vs. 4.5 % in the placebo group) and pruritus (7.1 % in the zoster group vs. 1.0 % in the placebo group), warmth (1.7 % vs. 0.3 %). The majority (app. 85 %) of reactions were mild (swelling or erythema reported maximum sizes of ≤2 inches). Usually, the median duration of reaction in the zoster group was about 4 days compared to 2 days in the placebo group.

The proportions of subjects reporting one or more systemic clinical AE in the 2 vaccination groups were similar (24.7 % for the zoster group vs. 23.6 % for the placebo group). The most frequently reported systemic clinical adverse experiences (≥2% in 1 or more vaccination groups) were headache, respiratory infection, and rash.

The incidence rates of the specific vaccine-related systemic clinical adverse experiences of fever, diarrhoea, headache, and maculopapular rash appeared to be numerically higher in zoster vaccine recipients when compared with placebo recipients. With the exception of headache (zoster vaccine group, 1.4%; placebo group, 0.9%), no statistically significant differences were observed between the 2 vaccination groups with respect to any reported vaccine-related systemic clinical adverse.

Protocol 007 (Post-dose 1) and Protocol 009

The purpose of Protocol 007 was to evaluate the safety profile of a 2-dose regimen of zoster vaccine in adults ≥60 years of age. The purpose of Protocol 009 was to evaluate the safety profile of a single dose of zoster vaccine at the intended maximum release potency in adults ≥50 years of age.

For the subjects receiving zoster vaccine in these studies, 72.8% reported one or more adverse experiences, compared with 43.8% of placebo recipients. The percentage of subjects reporting injection-site adverse experiences was greater in zoster vaccine recipients (60.2%) compared with placebo recipients (10.5%). In the zoster group the most common injection-site AEs (incidence ≥25%) were erythema, pain, and swelling. The other commonly reported adverse experience (incidence ≥5%) was pruritus.

In Protocol 009, the majority of injection-site adverse experiences in both vaccination groups were reported within 5 days post vaccination and were reported to be mild in intensity. In the higher potency vaccine group, the proportions of subjects reporting pain/tenderness (47.3 % in the high and 38.9 % in the low potency group) and swelling (41.2 % in the high and 32.9 % in the low potency group) were statistically significantly higher than in the lower potency vaccine group. A numerically higher rate of injection site pruritus (12.6 %) was observed in the zoster vaccine high potency group compared with the low potency group (9.0 %). The same trend was also seen for warmth. For all other injection-site AEs, the 2 groups were comparable.

The percentage of subjects reporting systemic clinical AEs was comparable after receiving zoster vaccine or placebo, but the percentage of subjects with vaccine related systemic clinical AEs was higher among zoster vaccine recipients. Nearly 40% of zoster vaccine recipients reported at least one systemic clinical adverse experience. The most frequently reported systemic clinical AEs in both studies (Protocol 007 post dose 1 and Protocol 009) (incidence ≥5% in zoster vaccine recipients) was headache (8.7%).

Other Protocols

Subjects enrolled in Protocol 001 and subjects enrolled in Protocol 002, as well as the VZV-seropositive subjects enrolled in Protocol 003, reported the same general pattern of adverse experiences as the subjects in Protocols 004, 007, and 009.

Adverse Experiences After a Second Dose of Zoster Vaccine

Across 4 clinical studies, Protocols 002, 005, and 007 and VARIVAX Protocol 049, a total of 481 subjects ≥50 years of age received a second VZV vaccination. The injection-site adverse experiences reported by subjects within Days 0 to 42 post-vaccination after receiving a second dose of zoster vaccine or PUVV were generally similar to the injection-site adverse experiences reported after an initial dose. The systemic clinical AEs reported by subjects within Days 0 to 42 post vaccination after receiving a second dose of zoster vaccine or PUVV were generally slightly lower in incidence and similar in spectrum to the systemic clinical AEs reported by subjects after an initial dose.

- Serious adverse event (SAE)/deaths/other significant events

SAE
In protocol 004 routine safety monitoring cohort(Days 0 to 42 post vaccination) including all subjects, the percentage of subjects with one or more systemic adverse events was 1.37 % in the zoster group and 1.36% in the placebo group. Only 5 serious adverse events (within 42 days after vaccination) were assessed by the investigators as at least possible vaccine-related; two were in the zoster vaccine group:

- A 80 year old man developed joint pain, swelling, and stiffness on day 3 post vaccination. He was later diagnosed with polymyalgiac rheumatica.
- A 64 year old woman with a history of asthma experienced an exacerbation of asthma on day 2 post vaccination.

Within the three placebo cases, there was one case of an anaphylactic reaction 90 minutes after administration of placebo. Information is insufficient to assess whether the AE was related to a pre-existing peanut allergy or caused by hydrolized porcine gelatin (used as a stabilizer and present in the placebo formulation).

The rates of HZ-related hospitalization in the zoster vaccine group (5 hospitalizations) and the placebo group (6 hospitalizations) were not different.
In protocol 007 and 009, a total of 10 subjects reported SAEs but none was determined by the investigator to be vaccine related.

Deaths
No deaths occurred in Protocols 001, 002, 003, 005, 007, and 009. In Protocol 004, the overall mortality rate in the zoster vaccine group was similar to that in the placebo group.

VZV-Like Rashes
The reported rates of non-injection-site varicella-like and HZ-like rashes within 42 days post vaccination were low (< 1 %) in both zoster vaccine recipients and placebo recipients in all of the clinical studies.
In Protocol 004, a total of 82 non-injection-site varicella-like (18 in the zoster and 14 in the placebo group) or HZ-like rashes (17 in the zoster and 33 in the placebo group) were reported. Lesion specimens from 45 HZ-like rashes and 11 varicella-like rashes were available for PCR testing. From these specimens, a diagnosis of HZ was confirmed for 5 subjects in the zoster vaccine group and 20 subjects in the placebo group. All varicella –like and zoster -like rashes that were VZV-positive by PCR were found to be due to wild-type VZV; the attenuated vaccine strain of VZV was not detected in any of these rashes.

- Laboratory findings

No laboratory safety tests were performed in any of the clinical studies.

- Safety in special populations

The number of recipients 50-59 years old is somewhat limited. The data indicate that the frequency of injection-site reactions is slightly higher than in the older age group.
The proportion of subjects with injection-site adverse experiences from Day 0 to 42 post vaccination was generally higher in the younger age group compared with the older age group. Specifically, the

proportions of subjects reporting injection-site erythema, pain/tenderness, and swelling were numerically greater among subjects in the younger age group.

- Safety related to drug-drug interactions and other interactions

No specific drug interactions were studied. No concomitant use with other vaccines have been studied. Study of concomitant administration with influenza virus vaccine is being conducted. Plan formal studies of concomitant use with other routinely administered adult vaccines were under evaluation.

- Discontinuation due to adverse events

Number of discontinuated subjects was very low. In all these studies only two subjects discontinuated because of vaccine related adverse event. These events were not serious.

- Post marketing experience

There is no postmarketing experience exists since Zoster vaccine was not yet been licensed in any country at the time of the assessment.

Post-marketing experience is solely available for, VARIVAX, a marketed Oka/Merck VZV vaccine (with a lower potency than ZOSTAVAX) typically administered to varizella history negative individuals who are younger than the target population for the zoster vaccine.

1.1 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system has deficiencies that should be addressed as part of the follow up measures.

Risk Management Plan

The MAA submitted a risk management plan.

No clinically important safety risks have been identified, nevertheless, there are missing information and some potential risks cannot be excluded.

Summary of the risk management plan

Safety issue	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Lack of data in immunocompromised subjects.	The Applicant will study the safety and immunogenicity in HIV-infected individuals and subjects on chronic systemic corticosteroid therapy.	Contraindications in primary and acquired immunodefiscuiency states, in case of immunosuppressive therapy or active untreated tuberculosis (see SPC section 4.3). Warnings in section 4.4 and 5.1 with regard to adults infected by HIV and subject with immunocompromised subjects.
Lack of data on concomitant administration of zoster vaccine and other authorised vaccines.	The applicant will provide results of a study of concomitant administration with influenza virus vaccine (protocol 011).	Warning in section 4.5 of the SPC
- Zoster-like or Varicella-like Rashes Temporally Associated With	Health care providers reporting these adverse experiences will be offered the opportunity to submit specimens to the Applicant's Varicella Zoster	- Information on zoster-like or varicella-like rashes are included in section 4.8 of the SPC.

Zoster Vaccine. - Potential Transmission of Oka/Merck Vaccine Virus Strain. - Inadvertent Exposure of Immunocompromised Individuals - Potential Central Nervous System Events	Virus Identification Program (VZVIP). Through this program, clinical specimens can be analyzed by PCR in order to determine whether an observed event is associated with the presence of wild-type VZV or of Oka/Merck vaccine virus. It is expected that by adding this additional measure to standard post-marketing reporting, it will be possible to get a clear picture of the adverse experiences that are associated with the presence of vaccine virus.	- Warning on transmission in section 4.4 of the SPC
Exposure to Zoster Vaccine During Pregnancy	The pregnancy registry for VARIVAX will be expanded to include ZOSTAVAX.	Contraindication in case of pregnancy (see section 4.3 of the SPC) and warmings in section 4.4 and 4.6 of the SPC.
Potential for allergic reactions to the active substance or to any excipients or trace of residuals (e.g. neomycine)	Routine pharmacovigilance	Contraindication and warnings (see sections 4.3 and 4.6 of the SPC).
Unknown duration of Protection and need for a booster dose, with theoretical possibility to shift the occurrence of HZ to an older age.	Study of long-term persistance of efficacy (extension of Protocol 004 and Protocol 013 which extends follow-up through 10 years postvaccination for about 7000 recipients)	

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

1.2 Overall conclusions, risk/benefit assessment and recommendation

Quality

During the evaluation of ZOSTAVAX no major objections were identified. Other minor concerns have been adequately addressed, however, several commitments are made by the applicant, and several follow-up measures are defined to provide further information post-approval. In conclusion, all quality issues are resolved.

Non-clinical pharmacology and toxicology

No non-clinical data were performed nor considered necessary in view of the experience with varicella live viral vaccines and the lack of relevant animal models.

Efficacy

Immune response to vaccination has been demonstrated, even if there is no established correlation with vaccine efficacy. Immune responses were shown to persist at least up to 36 months.

Clinical study 004 performed with ZOSTAVAX demonstrated that, compared to placebo, vaccination of adults, 60 years of age or older, with live attenuated (Oka/Merck) varicella zoster vaccine decreases the incidence of HZ (5.4 versus 11.1 per 1000 person-years) and PHN (0.5 versus 1.4 per 1000 person-years). The vaccine also showed efficacy with respect to the HZ "Burden of illness", which includes, besides the incidence of HZ, duration and severity of pain as an indicator of vaccine efficacy.

The effect of vaccination on both HZ BOI and incidence of PHN mainly results from the reduced incidence of HZ after vaccination. Nevertheless, since the VE_{BOI} is larger than the VE_{HZ} (61% vs 51%), it seems that vaccination may also influence the course/severity of HZ.

Vaccine efficacy in terms of HZ incidence was clearly better in the age group 60-69 years of age. However, a benefit from vaccination was also evident for older subjects, i.e. >70 years of age; although the reduction of HZ incidence was less prominent in this age group, there was, compared to younger individuals, a more pronounced effect of vaccination with respect to the duration of clinically significant pain (score ≥ 3) and severity of illness.

Long-term protection and need for a booster or a second dose will be further investigated, with considetation to age categories.

Data are missing in some patient populations such as mild and moderately immunocompromised subjects or subjects who reported having experienced a previous episode of HZ.

Safety

Based on a relatively large safety database consisting of more than 20 000 exposed individuals from controlled clinical trials with an average follow up time of about 3 years, ZOSTAVAX showed a good safety profile.

ZOSTAVAX was generally well tolerated in adults ≥60 years of age. The most commonly observed adverse reactions were injection site reactions and headache. Injection-site reactions were more frequent among zoster vaccine recipients compared to placebo recipients but they were generally mild in intensity and of short duration. The overall incidence of systemic clinical adverse events following a dose of zoster vaccine was similar to that following a dose of placebo.

Following a dose of zoster vaccine, both varicella-like rashes and zoster-like rashes are uncommon.

From the safety database the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

No clinically important safety risks have been identified, nevertheless, there is missing information and some potential risks cannot be excluded.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed them.

Different storage conditions of the lyophilized powder and the diluent

During the evaluation of ZOSTAVAX, the appropriateness of the applicant's approach on handling the different storage conditions for the lyophilized powder and the diluent has been extensively discussed at the Biologics Working Party, the Vaccine Working Party and CHMP.
The diluent is supplied together with the lyophilized powder to avoid that the vaccine is reconstituted with the wrong diluent (e.g. 0.9% NaCl solution for injection) or with the wrong volume of diluent. It is believed that this risk outweighs the potential risk of incorrect use or error caused by the different storage conditions of the vaccine components.
As the components of ZOSTAVAX cannot be stored together, a link between the lyophilized powder and the diluent is made through the text on the SPC, labeling and package leaflet, including a clear reference to each other and specific recommendation of use/method of administration. This is not a self-administered product and it is expected that reconstitution and administration by a health care professional according to the instructions ensure correct storage and use of the vaccine. In order to secure traceability of all the batches that have been shipped together and to maintain the link between active substance and diluent, the applicant will use a validated computerized system, which will assign a specific code for each combination that is shipped.
The applicant will also ensure that the expiry date of the diluent shipped with the active substance is at least equivalent to the expiry date of the active substance. If either component of the product has to be replaced (for ex. if a component has expired or if a component is missing) the applicant will provide a replacement of the complete product (active substance and diluent).
The applicant also pointed out that they currently market a frozen varicella vaccine presented in the same way as ZOSTAVAX on the Italian and US markets; in the US alone, over 40 million doses have been distributed over the past 10 years where the different storage conditions have been implemented in distribution centers, pharmacies, physician's practices and public health clinics. The CHMP considers that the distribution channels within the EU are comparable to the US ones.
Taking into account the above, the CHMP concludes that the company has provided a satisfactory justification for this approach and has implemented appropriate measures to ensure the safe and correct use of the vaccine.

Risk-benefit assessment

The live, attenuated strain of VZV (Oka/Merck strain) is a well-known vaccine strain. The difference of ZOSTAVAX as compared to the currently available Varivax is the more than tenfold higher potency.

In a population of ≥60 years of age, a single dose of ZOSTAVAX was shown to substantially reduce the risk of both herpes zoster and post-herpetic neuralgia over a period of about three years after vaccination. An effect was also observed in term of the severity and duration of zoster-related pain which is merely a consequence of the prevention of HZ and PHN.

It is unknown as how long the vaccine-induced immune response will offer protection or whether a second dose will be beneficial.

The current safety database suggests a good safety profile for the single dose regimen. No safety signals were observed.

The safety in immuno-compromised individuals remains to be established.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns;
- no additional risk minimisation activities were required beyond those included in the product information.

As a consequence, the benefit risk ratio of ZOSTAVAX for the prevention of herpes zoster ("zoster" or shingles) and herpes zoster related postherpetic neuralgia (PHN) in subject 60 years of age or older is considered positive.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of ZOSTAVAX in *the prevention of herpes zoster ("zoster" or shingles) and herpes zoster related postherpetic neuralgia (PHN*) *in individuals from 60 years of age* was favourable and therefore recommended the granting of the marketing authorisation.