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ZOSTAVAX™
(Zoster Vaccine Live [Oka/Merck])

Advisory Committee Meeting Background Document

Merck Research Laboratories

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Dear Ms. Walsh:

ZOSTAVAX™
(Zoster Vaccine Live [Oka /Merck])
STN 125123

Advisory Committee Meeting Background Document

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Questions concerning this should be directed to me at (484) 344-3149 or in my absence, Ercem Atillasoy, M.D. (484) 344-7811.

Sincerely,

David E. Gutsch, M.D.
Director
Worldwide Regulatory Affairs
Vaccines/Biologics

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FDA Advisory Committee
Briefing Document

Presented to:

Vaccines and Related Biological
Products Advisory Committee

December 15, 2005

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADL	Activities of daily living
ADLI	Activities of daily living interference
ANCOVA	Analysis of covariance
AUC	Area under the curve
BOI	Burden of illness
CEC	Clinical Evaluation Committee
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CMI	Cell mediated immunity
DM	Diabetes mellitus
ELISA	Enzyme-linked immunosorbent assay
GMCs	Geometric mean counts
GMFR	Geometric mean fold rise
GMTs	Geometric mean titers
gpELISA	Glycoprotein enzyme-linked immunosorbent assay
HZ	Herpes zoster
IL	Interleukin
IZIQ	Initial Zoster Impact Questionnaire
ITT	Intention-to-treat
MITT	Modified-intention-to-treat
MRL	Merck Research Laboratories
NIAID	National Institutes of Health-National Institute of Allergy and Infectious Disease
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PFU	Plaque-forming units
PHN	Post herpetic neuralgia
SFC	Spot-forming cell
SOP	Standard Operating Procedure
SPS	Shingles Prevention Study
VA CSP	Veterans Affairs Cooperative Studies Program
VE_{BOI}	Vaccine efficacy for burden of illness
VE_{HZ}	Vaccine efficacy for incidence of herpes zoster
VE_{PHN}	Vaccine efficacy for incidence of postherpetic neuralgia
$VE_{SADLI:HZ}$	Vaccine efficacy for substantial ADLI above-and-beyond VE_{HZ}
VRC	Vaccination Report Card
VZV	Varicella-zoster virus
VZV IFN-y ELISPOT	Varicella-zoster virus interferon-gamma enzyme-linked immunospot
VZV IP	Varicella-zoster virus Identification Program
ZBPI	Zoster Brief Pain Inventory

I. INTRODUCTION AND ORGANIZATION OF DOCUMENT

Merck Research Laboratories (MRL) has submitted a Biologics License Application for ZOSTAVAX™[1] [zoster vaccine live (Oka/Merck)], based largely on the results of the Shingles Prevention Study (SPS), a multicenter, randomized, placebo-controlled trial involving a total of 38,546 subjects, and on the results of additional supporting studies.

The results of these studies provide convincing evidence that ZOSTAVAX™ prevents herpes zoster (HZ) and its complications, notably postherpetic neuralgia (PHN), and reduces the severe pain associated with HZ.

Based on the data presented in the license application and summarized in this briefing document, the proposed indications for ZOSTAVAX™ are as follows:

ZOSTAVAX is indicated for:

- prevention of herpes zoster (shingles)

- prevention of postherpetic neuralgia (PHN)

- reduction of acute and chronic zoster-associated pain.

In addition, ZOSTAVAX™ is recommended for immunization of individuals 50 years of age or older.

The age indication is supported by epidemiologic data that speak to the medical need, as well as available age-related data with respect to efficacy, immunogenicity, and safety.

The Synopsis (Section II) that immediately follows this section provides a summary intended to orient the reader to the key elements of this document. The Synopsis is cross-referenced to the Comprehensive Background (Section III) where appropriate. Citations are not provided in the Synopsis but are included in the Comprehensive Background.

Throughout the text of this document, all protocols presented by number are ZOSTAVAX™ protocols (e.g., Protocol 004), unless otherwise noted (e.g., VARIVAX™[1] Protocol 049).

A list of references follows the conclusions (references are denoted in the text by numbers within brackets [ ]).

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[1] ZOSTAVAX and VARIVAX are trademarks of Merck and Co., Inc., Whitehouse Station, New Jersey, U.S.A.

II. SYNOPSIS

1. Introduction

The principal objective of the clinical development program for ZOSTAVAX™ was to develop an immunogenic and well-tolerated vaccine that would significantly reduce the incidence of HZ and PHN and the pain burden of illness (BOI) (defined as a composite measure of incidence, severity, and duration of pain) associated with HZ in older adults.

The 8 clinical studies in support of ZOSTAVAX™ were conducted from 1996 to 2004, and include 6 randomized, controlled clinical studies (Protocols 001, 002, 003, 004 [the Shingles Prevention Study], 007, and 009) and 1 open-label booster clinical study (Protocol 005). Five (5) of these clinical studies were placebo-controlled. Additional data from subjects ≥30 years of age who received ZOSTAVAX™ in VARIVAX™ Protocol 049 are also available.

The clinical efficacy of the zoster vaccine was demonstrated in the Shingles Prevention Study, a placebo-controlled study that enrolled subjects ≥60 years of age, in which a total of 38,546 subjects (19,270 in the ZOSTAVAX™ group and 19,276 in the placebo group) were randomized. The major efficacy endpoints of interest were reduction in the incidence of HZ, reduction in the incidence of PHN and reduction in the HZ pain burden of illness (BOI). Compared with placebo, ZOSTAVAX™ reduced the incidence of HZ, reduced the incidence of PHN, and reduced the BOI related to HZ pain. The prespecified success criteria were met for each of these 3 key endpoints that support the proposed indications for ZOSTAVAX™. Furthermore, the vaccine efficacy against the occurrence of HZ was observed to be greater for younger subjects (those 60 to 69 years of age) compared with older subjects (those ≥70 years of age) in the Shingles Prevention Study.

The clinical studies presented demonstrate that ZOSTAVAX™ elicits a varicella-zoster virus (VZV)-specific immune response in vaccinated individuals and that this immune response correlates with efficacy against the occurrence of HZ. Immune response was observed to be higher in younger subjects than in older subjects.

The overall safety results demonstrate that ZOSTAVAX™ is generally well tolerated, with no adverse experiences, other than injection-site reactions, occurring at a substantially higher frequency than following a dose of placebo.

The efficacy results of the Shingles Prevention Study support the proposed indications for prevention of HZ, prevention of PHN, and reduction of the pain burden associated with HZ. The data presented indicate that ZOSTAVAX™ is immunogenic and has an excellent safety profile. Although the Shingles Prevention Study enrolled subjects 60 years of age and older, support for the proposed target age range of ≥50 years of age is compelling, based on: (1) population-based studies that show a consistent, substantial increase in the incidence of HZ beginning at 50 years of age; (2) greater efficacy against HZ was seen for subjects 60 to 69 years of age, compared with subjects ≥70 years of age; (3) comparable immunogenicity results across the age range studied; and (4) an acceptable safety profile was in the 50- to 59-year-old age cohort in Protocol 009.

1.1   Product Description

ZOSTAVAX™ [zoster vaccine live (Oka/Merck)] is a single-dose, sterile, preservative-free, live, attenuated vaccine manufactured by Merck & Co., Inc. Each 0.65-mL dose of ZOSTAVAX™ contains a minimum of 19,400 plaque-forming units (PFU) of the Oka/Merck strain of VZV at expiry. The same manufacturing process used for ZOSTAVAX™ is used to manufacture VARIVAX™, the vaccine for the prevention of varicella (chickenpox), with the exception that ZOSTAVAX™ contains a higher potency of the attenuated Oka/Merck vaccine virus in order to elicit an appropriate immune response.

1.2   Background and Epidemiology (See Section III.1)

HZ causes a significant burden of disease in individuals ≥ 50 years of age, and is expected to increase as our population ages. Approximately 1 million cases of HZ occur every year in the United States. The annual risk of HZ begins to increase markedly around 50 years of age, rising sharply thereafter. The lifetime risk of HZ may be as much as 30% or higher, and as high as 50% in individuals who reach 85 years of age. Nearly all adults 50 years of age an older have had a primary VZV infection, and are at risk of developing HZ when VZV-specific immunity decreases with advancing age. HZ is characterized by a unilateral, vesicular cutaneous eruption with a dermatomal distribution. The incidence and severity of HZ increase markedly with age, and complications, which are relatively infrequent in otherwise healthy children and younger adults, occur in almost one-half of older individuals.

One of the most significant clinical manifestations of HZ is pain. Painful neuritis during the period of the acute rash occurs in over 90% of HZ sufferers. PHN, the neuropathy that accompanies HZ, occurs when pain persists in the area of the rash at a time beyond cutaneous healing. PHN, a major complication and cause of morbidity from HZ in the immunocompetent host, occurs on average in 10 to 20% of HZ patients. The frequency and severity of PHN increase with age, occurring in as many as 25 to 50% of HZ patients over 50 years of age. Published literature provides multiple definitions of PHN; for the purposes of the ZOSTAVAX™ clinical studies, PHN was defined rigorously, as any clinically significant pain (score ≥ 3 on a scale of 0 to 10, in which 0 = no pain and 10 = worst possible pain) present more than 90 days after HZ rash onset.

Among the other serious complications that may occur following HZ are cutaneous complications, ophthalmic HZ with ocular complications, and a variety of neurologic complications.

Serious morbidity can be associated with HZ and its complications; ~2 to 3% of HZ cases are hospitalized, including up to 10% of patients >65 years of age. In the United States, it is estimated that 12,000 to 19,000 individuals are hospitalized every year with a primary diagnosis of HZ, among an estimated total of 50,000 to 60,000 HZ-associated hospitalizations, most of these in immunocompetent individuals.

There is currently no medical treatment or procedure that prevents HZ. Antiviral agents, administered alone or combined with corticosteroids, when given shortly after HZ onset may modestly reduce the duration of the rash and the severity and duration of acute HZ-associated pain, but have limited impact of the risk of developing long lasting PHN.

A means of preventing HZ and its complications would therefore address an unmet medical need. Consequently, ZOSTAVAX™ has been developed for the prevention of HZ, prevention of PHN, and reduction of pain burden associated with HZ in individuals 50 years of age and older.

2. Clinical Development Program

2.1 Population Studied (See Section III.2.1)

The studies conducted in this clinical development program enrolled immunocompetent individuals, many of whom had concurrent, medically-stable chronic medical conditions that were typical of persons in the age groups studied. Protocols enrolled subjects 30 to 99 years of age. However, most studies enrolled subjects who were ≥60 years of age. Subjects were not prescreened for VZV serostatus, with the exception of VARIVAX™ Protocol 049 and ZOSTAVAX™ Protocol 003, which specifically targeted VZV-naïve individuals for enrollment.

Overall, 40,335 subjects ≥50 years of age were enrolled in ZOSTAVAX™ clinical studies with 20,697 of these subjects receiving zoster vaccine. The majority of the data come from the Shingles Prevention Study which enrolled subjects ≥60 years of age. Among a subset of Shingles Prevention Study subjects it was found that nearly 90% had one or more underlying medical conditions, and approximately 90% of subjects were taking one or more medications at the time of vaccination. The vaccination groups were generally comparable with regard to the number and percentage of subjects with specific prior conditions, as well as the general distribution of these conditions.

2.2 Clinical Efficacy (See Section III.3)

Success was demonstrated in both of the pre-specified co-primary endpoints, HZ pain BOI and PHN incidence, so overall, the Shingles Prevention Study was declared a success. Success was also demonstrated for vaccine efficacy in reducing the incidence of HZ and in reducing the severe pain that is associated with HZ and PHN.

Compared with placebo, ZOSTAVAX™ reduced the incidence of HZ (315 evaluable HZ cases [5.4/1000 person-years] in the ZOSTAVAX™ group, versus 642 [11.1/1000 person-years] in the placebo group). The estimated vaccine efficacy for incidence of herpes zoster (VE_{HZ}) was 51.3% (95% confidence interval [CI] = [44.2%, 57.6%]), exceeding the prespecified success criterion (lower bound of the 95% CI ≥ 25%). The reduction in HZ incidence was 63.9% (95% CI = [55.5%, 70.9%]) in subjects 60 to 69 years of age and 37.6% (95% CI = [25.0%, 48.1%]) in subjects ≥70 years of age. The higher efficacy in younger individuals (60 to 69 years of age versus ≥70 years of age) suggests that ZOSTAVAX™ would be at least as effective in the 50-to-59 age range as in older individuals.

PHN was defined as HZ-associated pain rated as ≥3 (on a 0 to 10 scale) persisting or appearing more than 90 days after the onset of the HZ rash. Compared with placebo, ZOSTAVAX™ reduced the incidence of PHN (27 PHN cases in the ZOSTAVAX™ group versus 80 PHN cases in the placebo group). The estimated vaccine efficacy for incidence of PHN (VE_{PHN}) was 66.5% (95% CI = [47.5%, 79.2%]), which met the prespecified success criteria (VE_{PHN} ≥62%; lower bound of the 95% CI >25%) for this endpoint. Statistical analyses using alternative time cutoffs to define PHN (pain present at least 30, 60, 120, and 182 days after rash onset) showed very consistent vaccine effects on PHN, with VE_{PHN} ranging from 58.9% to 72.9%.

The primary efficacy analysis of HZ-associated pain compared the HZ pain BOI score in the ZOSTAVAX™ group with that in the placebo group. The HZ pain BOI score was a composite endpoint incorporating the incidence, severity, and duration of HZ pain. As such, over the 182 days of clinical follow-up for HZ, the HZ BOI captures acute and chronic HZ-associated pain. A "worst pain" score was obtained using the validated Zoster Brief Pain Inventory (ZBPI) questionnaire. A worst pain score ≥3 is associated with an impact on quality of life and ability to carry out activities of daily living. For an individual subject who developed HZ, the severity-by-duration score of HZ pain was defined as the area under the worst pain response (rated on a 0-to-10 scale) versus time curve (AUC) during the 6-month period following HZ rash onset. For example, a subject experiencing a worst pain score of 10 for 30 days and worst pain scores of 0 for the remainder of the 6-month follow-up period would have a severity-by-duration score of 300. For subjects who did not develop HZ during the study, the individual HZ BOI score was defined as zero.

Compared with placebo, ZOSTAVAX™ significantly reduced the BOI related to HZ pain. The estimated vaccine efficacy for BOI (VE_{BOI}) was 61.1% (95% CI = [51.1%, 69.1%]), meeting the prespecified success criteria (VE_{BOI} ≥47%, lower bound of the 95% CI >25%).

Compared with the overall efficacy observed, ZOSTAVAX™ had preferential impact on HZ cases with severe pain. For example, the group with severity-by-duration scores >600 (e.g., with a maximal score of 10 for >60 days) included only 11 ZOSTAVAX™ recipients, compared with 40 placebo recipients, a reduction of 72.6% (95% CI: 45.7%, 87.3%). Also, among subjects who developed PHN (with pain ≥3 at least 90 days after HZ rash onset), the mean severity-by-duration scores through the end of HZ follow-up were much lower in the ZOSTAVAX™ group than in the placebo group (346.7 versus 805.2), a reduction of 57% (p=0.016). These results demonstrate that compared with placebo, ZOSTAVAX™ substantially reduced severe pain associated with HZ and PHN.

For both age cohorts, the observed HZ pain BOI and the incidence of PHN were both much lower in the ZOSTAVAX™ group than in the placebo group, and the vaccine efficacy was similar across the 2 age categories. Thus, for both of the study's co-primary endpoints, age did not have an impact on the protection afforded by the vaccine.

Another secondary efficacy endpoint that was prespecified in the second tier of the statistical analysis regarded the vaccine effect on the duration of clinically significant HZ pain (defined as the number of days between the first day after HZ 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). Compared with placebo, ZOSTAVAX™ reduced the duration of clinically significant pain associated with HZ (median in the ZOSTAVAX™ and placebo groups: 20 days versus 22 days; p-value<0.001).

ZOSTAVAX™ reduces the HZ pain interference with activities of daily living (ADL) by 66.2% (95% CI: 55.4%, 74.4%), when compared with placebo. Note that a large proportion of this reduction in the measure of ADL in the vaccine group results from the reduction of HZ incidence in that group. In a prespecified analysis to determine the vaccine efficacy on the incidence of substantial interference with ADL above-and-beyond vaccine efficacy for HZ, the 8.2% reduction in the risk of having substantial ADL interference was not statistically significant (p-value=0.341).

2.2.1 Duration of Efficacy (See Section III.3.1.5)

In the Shingles Prevention Study, subjects were followed for a mean 3.1 years; no subjects were followed for as long as 5 years. The efficacy decreased somewhat shortly after vaccination, but stabilized thereafter. Based on the available data, the vaccine has demonstrated continuing efficacy through Year 4 postvaccination. Long-term efficacy of the vaccine is being evaluated at a subset of 12 the Shingles Prevention Study sites.

2.3 Summary of Immunogenicity Results (See Section III.3.2)

The immunogenicity data to support licensure of ZOSTAVAX™ were derived from the Shingles Prevention Study (Protocol 004) and Protocols 001, 002, 003, 005, 007, and VARIVAX™ 049. Overall, the data presented in this section demonstrate that ZOSTAVAX™ is immunogenic.

The key validated assays used to measure VZV-specific immunity in the ZOSTAVAX™ development program were the glycoprotein enzyme-linked immunosorbent assay (gpELISA) and the VZV interferon-gamma enzyme-linked immunospot (VZV IFN-γ ELISPOT) assay. The gpELISA has been used for many years in the development programs for Oka/Merck varicella vaccines. The response detected by the gpELISA is T-cell dependent, and so this assay, as well as the VZV IFN-γ ELISPOT assay, were used in the ZOSTAVAX™ program as candidate immunologic correlates of protection.

The key immunologic endpoints for studies conducted in this program were based on the geometric mean titers (GMTs) in the gpELISA and geometric mean counts (GMCs) in the VZV IFN-γ ELISPOT assay. For both assays, the ratio of the immune responses (ZOSTAVAX™ group to placebo group) at 6 weeks postvaccination and the geometric mean fold rise (GMFR) from baseline to 6 weeks postvaccination were also evaluated.

Individuals in the target population for ZOSTAVAX™ generally have high baseline VZV antibody titers in the gpELISA. Nonetheless, following a dose of ZOSTAVAX™, 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 Cell-Mediated Immunity (CMI) Substudy of the Shingles Prevention Study, a subset of 1395 subjects, the estimated GMTs at 6 weeks postvaccination were 478.7 gpELISA units/mL (GMFR from baseline, 1.7) in the ZOSTAVAX™ group and 287.8 gpELISA units/mL (GMFR from baseline, 1.0) in the placebo group. Furthermore, in this and other ZOSTAVAX™ clinical studies, the immune response as measured by estimated GMTs at 6 weeks postvaccination and by GMFR from baseline was at least as good in younger subjects as in older subjects.

VZV IFN-γ ELISPOT assay results are available from the CMI Substudy of the Shingles Prevention Study, and from Protocols 005 and 007. For the CMI Substudy population, the 6-week postvaccination response in the ZOSTAVAX™ group was significantly higher than in the placebo group, in terms of the GMC (69.8 spot-forming cells [SFC]/10^6 peripheral blood mononuclear cells [PBMC] in the ZOSTAVAX™ group, 31.8 SFC/10^6 PBMC in the placebo group) and the GMFR from Day 0 (2.1 in the ZOSTAVAX™ group, 0.9 in the placebo group). The estimated fold differences for both GMC and GMFR between the ZOSTAVAX™ and placebo groups were 2.2 (95% CI = [1.9, 2.5]).

In order to evaluate whether the vaccine-induced, VZV-specific immune responses correlated with protection against HZ, responses for CMI Substudy subjects by VZV IFN-γ ELISPOT assay and gpELISA were analyzed according to HZ status. VZV-specific immune responses by both assays correlated with protection against HZ, with the VZV antibody response by gpELISA at 6 weeks postvaccination demonstrating better correlation than the VZV IFN-γ ELISPOT 6 weeks postvaccination response.

In summary, as measured by gpELISA or by VZV IFN-γ ELISPOT, ZOSTAVAX™ elicits an immune response that is correlated with efficacy against HZ.

2.4 Clinical Safety (See Section III.4)

ZOSTAVAX™ builds on the excellent safety experience that has been observed with VARIVAX™. The VARIVAX™ program provides 10 years of postmarketing safety data, with over 56 million doses distributed. In the VZV-naïve population for which VARIVAX™ is intended, one would expect the greatest safety concern to be from adverse experiences that reflect the replication of the attenuated vaccine virus, such as varicella-like rashes or fever. Despite these potential concerns, VARIVAX™ has demonstrated an outstanding safety record, and these findings provide reassurance regarding the use of ZOSTAVAX™ in VZV-naïve older adults.

In contrast to the target population for VARIVAX™, ZOSTAVAX™ is intended for older adults with pre-existing immunity to VZV. In these persons, one would expect that the vaccine virus would be rapidly dealt with by an anamnestic immune response, and that common adverse experiences might be limited to injection-site reactions. The data presented in this document confirm the excellent safety profile of ZOSTAVAX™.

The clinical studies included in this Application enrolled a total of 40,335 subjects ≥50 years of age, of whom 20,697 received the zoster vaccine. The safety results from the pivotal efficacy trial were consistent with those of other ZOSTAVAX™ studies; across all studies, no safety signals of concern were noted. The only clinically significant difference observed between vaccine recipients and placebo recipients was an increase in the proportion with local adverse experiences, most of which were reported as mild. The incidence of elevated oral temperature (≥101.0°F; ≥38.3°C) was <1% in both vaccine recipients and placebo recipients. In the pivotal efficacy trial, headache was the only vaccine-related systemic clinical adverse experience seen more often in vaccine recipients than in placebo recipients (1.4% versus 0.9%). In general, the systemic clinical adverse experience profiles were comparable between ZOSTAVAX™ and placebo.

The safety profile of ZOSTAVAX™ was generally similar over a wide range of potencies. At the upper end of the anticipated clinical potency range, a modest increase in injection-site reactions was seen, compared with vaccine at a lower potency. However, the proportion of subjects reporting moderate or severe local reactions was lower than a prespecified, historical benchmark.

No safety concern was evident when ZOSTAVAX™ was administered to the small number of VZV-seronegative subjects who were identified in large, concerted serologic screening efforts, including in tropical countries. The reported rates of injection-site adverse experiences, systemic clinical adverse experiences, and elevated temperatures in these subjects were generally similar to the rates reported by the VZV-experienced subjects. The available data suggest that VZV-seronegativity is quite uncommon among older adults, but that no safety concern was evident.

3. Summary of Benefits and Risks (See Section III.5)

The results of the large scale, double-blind, randomized, placebo-controlled, multicenter efficacy study support the proposed indications for prevention of HZ, prevention of PHN, and reduction of the burden of pain associated with HZ.

No clinically important safety risks have been identified with the use of ZOSTAVAX™. Data from the 20,841 subjects who received ZOSTAVAX™ in clinical studies confirm that the vaccine has an excellent safety profile. Beyond injection-site reactions, which are to be expected in association with any vaccine, and headache in the Shingles Prevention Study, no adverse experiences were observed among ZOSTAVAX™ recipients at a frequency substantially higher than that among placebo recipients.

Prevention and optimal treatment for HZ and PHN present a significant unmet medical need. No satisfactory preventive options are currently available. Early initiation of treatment with an antiviral agent has been shown to reduce the severity of acute HZ and the duration of HZ-associated pain. Although prompt initiation of antiviral therapy may shorten the duration of PHN, the effect on PHN incidence and severity is uncertain. Therapeutic interventions often have only modest effects on established PHN, and they often are associated with high rates of adverse events, especially in the elderly.

In addition to being difficult medical conditions to manage effectively, HZ and PHN are more common than is widely appreciated. An estimated 1 million cases of HZ occur annually, and the estimated prevalence of PHN is at least 500,000 in the United States.

Every year, HZ is diagnosed in an estimated 50,000 to 60,000 hospitalizations (12,000 to 19,000 with a primary diagnosis of HZ) in the United States, with an average length of stay of approximately 5 to 7 days. Given the often unsatisfactory results associated with treatment, and the prospect of debilitating, chronic pain, the impact of ZOSTAVAX™ in the pivotal efficacy study is notable. Compared with placebo, ZOSTAVAX™ lessened acute-and-chronic pain (corresponding to the pain BOI during 6 months of follow-up) by more than 60%, reduced the incidence of HZ by more than one-half, and reduced the incidence of PHN by two-thirds.

Because a large majority of the vaccine doses in the Shingles Prevention Study were administered near the projected expiry potency, efficacy can be inferred throughout the range of potencies that are proposed during the vaccine's shelf life. Also, despite aggressive HZ and PHN case management in the Shingles Prevention Study with antivirals and analgesics, the benefits of ZOSTAVAX™ were still very dramatic. In these respects, the efficacy trial gave a realistic, perhaps even conservative assessment, of the benefit of a vaccine as it would be experienced in routine clinical practice.

Although the pivotal efficacy study included only subjects ≥60 years of age, epidemiological and clinical trial data presented in this document provide strong support for adopting 50 years as the age at which routine ZOSTAVAX™ vaccination should begin. The sharp age-related increase in HZ incidence begins in the sixth decade of life (i.e., 50 to 59 years of age), with an approximate doubling of the incidence relative to that for persons 40 to 49 years of age. An estimated 200,000 cases of HZ occur every year in the United States in individuals 50 to 59 years of age, i.e., ~21% of all HZ cases. In comparison, ~40% of all HZ cases occur in individuals ≥60 years of age. Therefore, vaccination beginning at 50 years of age (rather than at 60 years of age) could increase by approximately 50% the number of HZ cases that could be prevented or ameliorated with routine vaccination. In the Shingles Prevention Study, VE_{HZ} was higher (64%) in subjects 60 to 69 years of age than in subjects ≥70 years of age (38%). Thus, the overall VE_{HZ} of 51% is likely to be a conservative estimate for the 50-to-59 year age category. A similar effect was observed with respect to the immune response to ZOSTAVAX™, with

enhanced responses in younger individuals. That ZOSTAVAX would be generally safe and well tolerated in individuals 50 to 59 years of age could be predicted from the vast experience with VARIVAX™ and the results of Protocol 009. In Protocol 009, in which 185 subjects between 50 and 59 years of age were enrolled, ZOSTAVAX™ was well tolerated, although injection-site reactions of mild and moderate intensity were reported at a somewhat higher rate in subjects 50 to 59 years of age than in subjects ≥60 years of age. The potential safety risk in this age group is minimal, based on the available data.

In addition to the substantial medical impact, vaccinating younger adults could prevent work productivity loss, because the majority of individuals (~70% in the United States) 50 to 59 years of age are employed. Assuming an average of 3 to 5 days of work lost per HZ case (likely to be a conservative estimate), an estimated 400,000 to 700,000 work days are lost due to HZ every year among 50- to 59- year-olds alone in the United States.

In the Shingles Prevention Study, the efficacy remained relatively stable through Year 4 postvaccination, after a very early initial drop. Although the duration of the effect and the potential need for a "booster" dose remain unknown, a long-term persistence study to follow subjects from the Shingles Prevention Study for an additional 5 years is beginning in the fall of 2005.

Overall, ZOSTAVAX™ demonstrated strong evidence of efficacy in a population that was representative of the population for which it is intended, without an offsetting safety risk. The vaccine has demonstrated a favorable benefit/risk ratio.

III. COMPREHENSIVE BACKGROUND

1. Epidemiology and Treatment of Herpes Zoster and Postherpetic Neuralgia

After recovery from primary VZV infection, chickenpox, the virus remains latent in sensory ganglia. HZ is caused by the reactivation of latent VZV. It has been postulated that latent virus may reactivate subclinically following primary infection. This subclinical reactivation may form the basis for endogenous (natural) boosting of immunity in the absence of clinical manifestations of disease [1; 2]. However, in some individuals, reactivation and replication of the virus will cause HZ, perhaps due to waning VZV-specific CMI as a consequence of advancing age or various forms of immunosuppression [3; 4; 5]. HZ is characterized by a unilateral, vesicular cutaneous eruption with a dermatomal distribution that generally corresponds to the area of skin innervated by a single spinal or cranial sensory ganglion. The vesicles typically pustulate and crust in 7 to 10 days, but may take up to a month to heal. Viable virus can be present in lesions until crusting. Progression of the eruption to scabbing may be attenuated by the administration of antiviral drugs [3; 4; 6].

Anybody who has had a primary VZV infection, typically acquired in childhood or adolescence, is at risk of developing HZ with increasing age. In immunocompetent individuals, age is the main risk factor for developing HZ. The incidence and severity of HZ increase markedly with advancing age [7; 8; 9; 10] and complications, which are relatively infrequent in otherwise healthy children and younger adults, occur in almost one-half of older individuals [3; 4; 6; 11; 12; 13; 14; 15]. In the United States, Canada, and Europe, the overall annual incidence of HZ has been consistently estimated to be 3 to 4 per 1000 population [13; 14; 16; 17; 18; 19; 20; 21; 22]. Based on rates determined from a recent study, approximately 1 million cases of HZ occur every year in the United States (298 million population in 2005) [19].

The annual risk of HZ begins to increase markedly around 50 years of age, rising sharply thereafter, to more than 10 per 1000 annually among persons over 75 years of age (Hope-Simpson's landmark paper on HZ epidemiology: Figure 1). In Western, industrialized countries, approximately two-thirds of HZ cases occur in individuals older than 50 years of age [14; 16; 18]. The lifetime risk of HZ has been reported to be 10 to 20% in the general population [8; 9; 10], although calculations from recent incidence studies suggest that the true lifetime risk may be as much as 30% or higher [13; 14; 19; 23]; and as high as 50% in individuals who reach 85 years of age [3].

Figure 1

Herpes Zoster, Postherpetic Neuralgia and Age of Patient
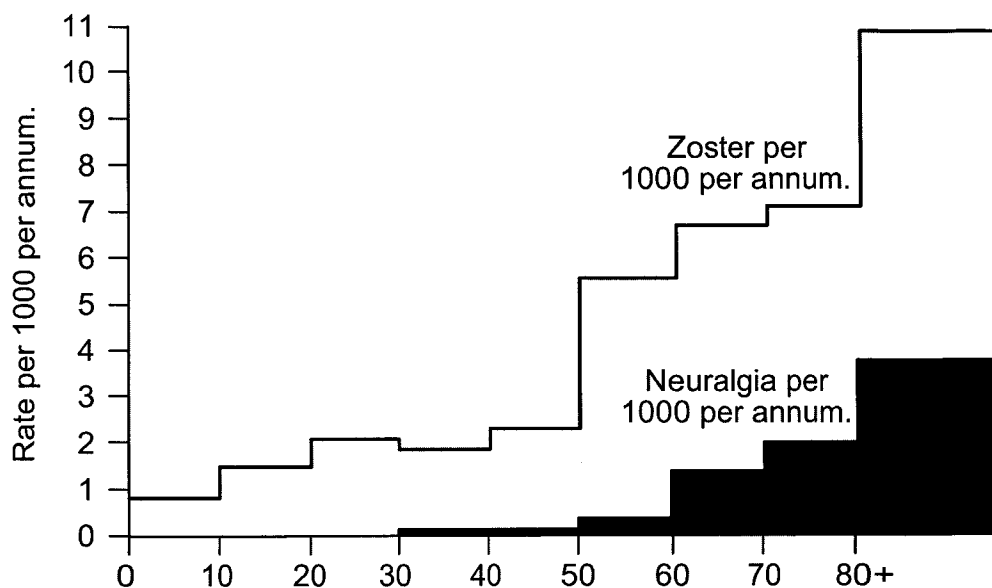
[14]

Immunocompetent persons may rarely suffer 2 or more episodes of HZ. The rate of recurrence, which is not well documented in the literature, has been reported to range from 1.5 to 12.5% of HZ patients [3; 4; 13; 24].

One of the most significant clinical manifestations of HZ is pain, which is caused by damage and resulting histological and functional changes in neural tissues involved with pain transduction, transmission, and modulation. The relative contributions of direct viral effects and the immune response in the development of this neural damage are unclear. 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, or for a prolonged period of time after onset (PHN) [25; 26].

During the prodromal period of HZ, viral replication and the resulting immune response damage the sensory ganglion. Centrally, the infection and inflammation may extend to adjacent areas of the spinal cord; peripherally, nerve involvement may extend to the skin. VZV replicates in the affected skin and is detectable at the onset of the cutaneous lesions. This additional replication can further increase and prolong the pain caused by nerve injury, and add a skin-related component to the dermatomal pain [27; 28].

PHN occurs when pain persists in the area of the rash beyond cutaneous healing. PHN constitutes a major complication and cause of morbidity from HZ in the immunocompetent host. Although various definitions of PHN have been used in published work, mathematical modeling and contemporary consensus indicate that the definition should consider PHN as the presence of significant pain remaining or arising 90 days or more after rash appearance [29; 30; 31; 32]. No single, commonly agreed-upon definition of PHN exists in the medical community, especially with regard to the time point at which HZ-associated pain becomes PHN. PHN definitions in the literature have included pain of any intensity beyond the following time points: rash crusting/healing, or 1, 1.5, 2, 3, 4, or 6 months after either rash onset or rash crusting/healing [29; 30; 32; 33; 34; 35; 36; 37; 38; 39; 40; 41; 42; 43; 44]. On average, PHN occurs in 10 to 20% of HZ patients [3; 17; 18; 21; 45]. The frequency and severity of PHN increase with age, occurring in as many as 25 to 50% of HZ patients over 50 years of age [46; 6; 15; 7; 9; 47; 48; 40; 24]. The anatomic and functional changes responsible for PHN appear to be initiated early in the course of HZ, perhaps even during the prodromal period. This early development of neural changes responsible for PHN may explain why antiviral therapy, corticosteroids, and other treatments have only limited utility in preventing the occurrence of PHN, even if initiated promptly after the appearance of the skin lesions.

Patients with PHN describe characteristic patterns of pain, with the majority experiencing at least 2 of the following patterns: (1) spontaneous, constant, deep burning, throbbing, aching pain; (2) intermittent sharp, stabbing, shooting, lancinating pain, which may also be spontaneous; and (3) allodynia (pain from an innocuous stimulus) that usually lasts well beyond the duration of the stimulus (hyperpathia). Allodynia, which is present in at least 90% of PHN patients, is typically described as the most distressing and debilitating component of the illness [28].

Among immunocompromised hosts, the risk of disseminated HZ, with its associated severe morbidity and even death, is increased. Disseminated HZ, which can develop by either cutaneous extension to adjacent dermatomes or hematogenous spread, carries a mortality rate of 20 to 40% in immunosuppressed recipients of solid organ and bone marrow transplants [28]. A generalized skin eruption without a dermatomal distribution may appear clinically as varicella. Visceral complications can arise from neural extension or hematogenous dissemination of VZV, and can include hepatitis and pneumonitis, both of which may be life-threatening.

A number of other serious complications may occur following HZ [27; 28]. Cutaneous complications can occur among previously healthy patients; bacterial superinfection can lead to pronounced scarring, cellulitis, superficial gangrene, septicemia, pneumonia, and/or death. Ophthalmic HZ can result in corneal ulceration, vision impairment, and blindness; ocular complications include conjunctivitis, keratitis, uveitis, retinal necrosis, and panophthalmitis.

Neurologic complications in addition to PHN have been reported in association with HZ. Segmental motor paresis or paralysis has been reported to occur in ≥5% of HZ patients, and may involve the cranial nerves, as well as the extremities. Subclinical paresis probably occurs in an even larger number of cases [49]. Involvement of the facial or auditory nerves may result in development of Ramsay Hunt syndrome, which consists of HZ of the auditory meatus, ipsilateral facial palsy, and loss of taste in the anterior two-thirds of the tongue. Herpesviruses, including VZV, may be the cause of some cases of Bell's palsy that were previously considered idiopathic [50]. Other neurologic complications include anesthesia in the affected dermatome, Guillain-Barré syndrome, aseptic meningitis, transverse myelitis, meningoencephalitis, or autonomic nerve palsy that can result in neurogenic bladder dysfunction, ileus with intestinal obstruction, or rectal incontinence. Weeks to months following ophthalmic HZ, granulomatous cerebral angiitis may occur and cause a contralateral hemiplegia; a mortality rate of ~25% has been reported among patients who develop this uncommon complication [51].

Serious morbidity can be associated with HZ and its complications; ~2 to 3% of HZ cases are hospitalized, including up to 10% of patients >65 years of age [23; 52]. Recent data from state hospitalization databases indicate that the annual rate of hospitalization with a primary diagnosis of HZ ranges from 4 to 6.5 per 100,000 population [53]. Approximately 70 to 80% of these hospitalizations occur in individuals ≥50 years of age [53; 23; 54; 55]. Of note, 70 to 80% of all patients hospitalized with HZ, whether as primary diagnosis or not, are immunocompetent [53; 54]. In the United States, it is estimated that 12,000 to 19,000 individuals are hospitalized every year with a primary diagnosis of HZ, among an estimated total of 50,000 to 60,000 HZ-associated hospitalization [53]. The true rate of HZ-related hospitalizations may be even higher, because hospitalizations due to an HZ complication may not have an HZ diagnosis code.

With advanced age, HZ may become life-threatening. Recent data from countries that have implemented an improved classification of primary cause of death (e.g., death from HZ in immunocompromised patients is assigned to the underlying condition, not to HZ) estimate the annual mortality rate due to HZ to be 0.6 to 1.0 per million population, with almost all deaths occurring in persons >65 years of age [16; 54; 56]. In the United States, reported deaths with an underlying cause of HZ ranged from 123 to 152 in 1999 to 2001, with 80% occurring in individuals >65 years of age [57]. In addition, it has been suggested that deaths in individuals >50 years of age that are listed as due to varicella, may actually be deaths due to disseminated HZ that have been misclassified [58].

Despite the availability of antiviral agents to treat HZ, and a variety of medications and other therapies to help control the associated pain, HZ and its complications represent a large and growing medical problem among older adults. There is currently no medical treatment or procedure that prevents HZ. When given within 72 hours of rash onset, antiviral agents taken for 7 to 14 days may reduce although, modestly, the duration of the rash and the severity and duration of acute HZ-associated pain. Antiviral agents alone or combined with corticosteroids, may reduce the duration of pain but have limited impact of the risk of developing long lasting PHN. Therefore, even if treated early, HZ patients often experience significant acute and chronic pain. In addition, antiviral therapy is not indicated for HZ patients who seek care beyond 72 hours after rash onset. As a result, up to 25 to 50% of HZ patients over 50 years of age continue to experience PHN. ZOSTAVAX™ offers the hope of sparing a significant number of individuals from ever experiencing HZ and its complications. Along with the elimination of a large fraction of the pain and suffering due to HZ, ZOSTAVAX™ provides the possibility of eliminating half of the antiviral use for acute HZ and more than half of the numerous medications and procedures, which produce limited success and tolerability concerns for PHN, an often debilitating condition that can last for years. An effective means of preventing HZ and its complications would therefore address a pressing, unmet medical need. Consequently, ZOSTAVAX™ has been developed for the prevention of HZ, prevention of PHN, and reduction of the pain burden associated with HZ in individuals 50 years of age and older.

2.   Clinical Development Program

The success of an inactivated VZV vaccine in pilot studies conducted among immunocompromised patients for the prevention of HZ-associated pain and PHN, the promising immunogenicity findings in early clinical studies, and the low frequency of recurrent cases of HZ in immunocompetent people suggested that vaccination to prevent HZ and its complications was possible. These early pilot studies determined that a vaccine could elicit a VZV-specific immune response in older adults and immunocompromised patients, and was thus potentially able to mitigate the severity of HZ and its complications.

Beginning in the 1980s, Phase I/II studies sought to evaluate the safety, tolerability, and immunogenicity of a VZV vaccine among older adults. Vaccine lots of different potencies, as well as heat-inactivated lots, were tested in the clinic setting.

Table 1 provides a summary of the design of the more recent clinical studies that support the ZOSTAVAX™ license application in a tabular presentation that includes the study number and title, the target and actual vaccine potencies, the dates and locations in which the studies were conducted, the sample sizes, and the study objectives. The studies included in the development of ZOSTAVAX™ were conducted over a period of years (1996 to 2004) and with outside collaborators. In support of ZOSTAVAX™, the vaccine was assessed in 6 randomized, controlled clinical studies (Protocols 001, 002, 003, 004 [the Shingles Prevention Study], 007, and 009) and 1 open-label booster clinical study (Protocol 005). Five (5) of these clinical studies were placebo-controlled. Additional data from subjects ≥30 years of age in VARIVAX™ Protocol 049 are also available, from the clinical development program for VARIVAX™.

Table 1

Administrative Information of the Clinical Studies Supporting the Licensure of ZOSTAVAX™

Protocol Number	Study Title	Targeted Potency (Actual per Dose)	Location and Dates	Total Enrolled	Primary Study Objectives
001	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	~2000 to ~67,000 PFU/dose (1915 to 67,125 PFU/0.5 mL)	U.S.A. 04-Nov-1996 to 14-Jul-1997	276	(1) The primary objective of the study was to evaluate the safety and tolerability profile of the 6 vaccine lots with varying potencies in healthy, VZV-seropositive subjects 60 years of age and older.
002	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	~34,000 or ~50,000 PFU/dose (35,388 to 48,911 PFU/0.5 mL)	U.S.A. 09-Feb-1998 to 01-Jun-2001	398	(1) The primary objective for the first dose (Protocol 002-01) was to select a vaccine potency formulation that was safe and well tolerated in VZV-seropositive adults >60 years of age with or without chronic illnesses such as COPD or DM. (2) The primary objective for the second dose (Protocol 002-02) was to assess the safety of the vaccine as a second vaccination given to subjects who had previously received 1 dose of varicella-zoster vaccine.
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	~50,000 PFU/dose (48,800 PFU/0.5 mL)	Latin America and the Philippines 25-May-1998 to 04-Feb-1999	1148	(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 (Shingles Prevention Study)	Trial of Varicella-Zoster Vaccine for the Prevention of Herpes Zoster and its Complications	~19,000 to ~60,000 PFU/0.5 mL (21,481 to 61,834 PFU/0.5 mL)	U.S.A. 06-Nov-1998 to 30-Apr-2004	38,546	(1) To determine whether immunization with zoster vaccine can reduce the incidence and/or severity of HZ and its complications, primarily PHN, in persons 60 years of age and older.

Table 1 (Cont.)

Administrative Information of the Clinical Studies Supporting the Licensure of ZOSTAVAX™

Protocol Number	Study Title	Targeted Potency (Actual per Dose)	Location and Dates	Total Enrolled	Primary Study Objectives
005	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	~50,000 PFU/dose (46,290 PFU/0.5 mL)	U.S.A. 07-Jul-1999 to 27-Mar-2000	196	(1) To assess the safety of ZOSTAVAX™ given to subjects who have previously received 1 or 2 dose(s) of varicella vaccine.
007	A Double-Blind, Placebo-Controlled, Randomized Study to Evaluate Safety, Tolerability, and Immunogenicity After 1 and 2 Doses of Zoster Vaccine	~25,550 PFU/dose (22,925 PFU/0.5 mL)	U.S.A. and the Netherlands 12-Nov-2001 to 24-Feb-2003	210	(1) The primary objective of the study was to compare the VZV IFN-γ ELISPOT response ~6 weeks after 1 and 2 doses of zoster vaccine with the VZV IFN-γ ELISPOT response ~6 weeks after 1 and 2 doses of placebo.
009	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	~207,000 PFU (203,244 PFU/0.65 mL) or ~58,000 PFU (56,845 PFU/0.65 mL)	U.S.A., Canada, and Europe 30-Oct-2003 to 07-Jun-2004	698	(1) 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	Multicenter, Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 2-Dose Regimen of High-Titered (~50,000 PFU/0.5 mL) PUVV in Subjects ≥13 Years of Age	~50,000 PFU/dose of ZOSTAVAX™ (48,911 PFU/0.5 mL)	U.S.A., Colombia, and Italy 05-Apr-1999 to 30-Apr-2001	1366	(1) To determine if ZOSTAVAX™ will yield a similar immune response as VARIVAX™ 6 weeks after the second dose. (2) To assess the safety and tolerability of ZOSTAVAX™ after Doses 1 and 2.

2.1   Population

The studies conducted in this clinical development program enrolled immunocompetent individuals, many of whom had concurrent, medically-stable chronic medical conditions that were typical of persons in the age groups studied. Protocols 001, 002, 004 (the Shingles Prevention Study), 005, and 007 enrolled subjects who were ≥60 years of age. Protocol 009 enrolled subjects who were ≥50 years of age. Subjects enrolled in Protocols 001, 002, 004, 005, 007, and 009 were not prescreened for VZV serostatus. Inclusion criteria for these protocols required subjects have a history of varicella or long-term residence in a region with endemic varicella transmission; subjects were presumed to be VZV-seropositive on that basis. As a preliminary assessment of ZOSTAVAX™ prior to embarking on the Shingles Prevention Study, Protocol 002 specifically targeted subjects with diabetes mellitus (DM) or chronic obstructive pulmonary disease (COPD).

In an attempt to maximize recruitment of VZV-seronegative subjects, Protocol 003 enrolled subjects in tropical countries who were ≥30 years of age. 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. Because Protocol 003 and VARIVAX™ Protocol 049 targeted VZV-naïve individuals, subjects were prescreened for VZV serostatus.

A total of 20,841 subjects ≥30 years of age were vaccinated with at least one dose of ZOSTAVAX™. Of this total, 144 subjects were 30 to 49 years of age and 20,697 subjects were ≥50 years of age. Additionally, 598 subjects received a second dose of the vaccine. Among those receiving a second dose, 481 subjects were ≥50 years of age and 117 subjects were 30 to 49 years of age.

The majority of the ZOSTAVAX™ data are from the Shingles Prevention Study. Information on prior medical history was collected for subjects who participated in the Adverse Event Monitoring Substudy. Nearly 90% of these subjects had one or more underlying medical conditions, including such illnesses as hypertension (41.4% across both vaccination groups), angina pectoris/coronary artery disease (9.6%), diabetes mellitus (8.9%), arthritis (27.7%), depression (6.5%), and asthma/emphysema (4.6%). Subjects reported a variety of other common, as well as less common, conditions in frequencies generally reflective of a population of this age. The vaccination groups were generally comparable with regard to the number and percentage of subjects with specific prior conditions, as well as the general distribution of these conditions. Consistent with the high frequency of underlying medical conditions, approximately 90% of subjects in the Adverse Event Monitoring Substudy were taking one or more medications at the time of vaccination.

The Shingles Prevention Study, although conducted by the Veterans Administration, enrolled more than 15,000 women (41% of the total enrollment). Supportive analyses of potential covariates do not indicate any significant differences by gender in any of the efficacy outcomes in the study. There was also no evidence of any difference in vaccine efficacy across racial groups in the study.

3.   Clinical Efficacy

Section 3.1 presents overall clinical efficacy, the primary and other key endpoints, clinical relevance of efficacy data, and efficacy conclusions. Clinical efficacy of ZOSTAVAX™ was demonstrated in the pivotal Shingles Prevention Study. The population evaluated in the Shingles Prevention Study was representative of the intended older adult population for this vaccine.

The Shingles Prevention Study was a randomized, double-blind, placebo-controlled, multicenter study to determine whether vaccination of adults ≥60 years of age with ZOSTAVAX™ could decrease the incidence and/or severity of HZ and its complications, including PHN. The Shingles Prevention Study was conducted under collaborative research agreements between Merck & Co., Inc., the Department of Veterans Affairs Cooperative Studies Program (VA CSP), West Haven, Connecticut, USA and the National Institutes of Health--National Institute of Allergy and Infectious Diseases (NIAID). The subjects were randomized to receive either ZOSTAVAX™ or placebo in a 1:1 ratio. The randomization was stratified by 2 age groups (60 to 69 years of age, ≥70 years of age). The data from this clinical study demonstrated that compared with placebo, ZOSTAVAX™ was highly efficacious in preventing HZ and PHN, reducing the HZ pain BOI scores, and shortening the duration of clinically significant HZ pain.

All subjects enrolled in the Shingles Prevention Study were followed for the development of suspected HZ, beginning on the day after vaccination. Suspected cases of HZ were to be clinically evaluated within 24 hours of the first reported symptom, and then entered into protocol-specified follow-up. Subjects who were evaluated within 72 hours of rash onset were offered famciclovir. HZ pain was managed according to the judgment of the study site investigator. The case definition of a suspected case of HZ was purposely broad to ensure capture of mild/atypical cases, as well as classic HZ cases.

All suspected HZ cases (including those for which a final determination was ultimately made by laboratory data and those cases that were ultimately not determinable) were clinically adjudicated according to a Standard Operating Procedure (SOP) by a blinded, 5-member Clinical Evaluation Committee (CEC) who did not have access to laboratory data. Adjudication was based solely on the blinded clinical information. Suspected rashes that were determined not to be caused by HZ or were indeterminate were labeled "non-evaluable cases" according to the algorithm; confirmed cases were labeled "evaluable cases".

Lesion specimens were to be collected from all suspected HZ cases at the time of the first evaluation for VZV detection by polymerase chain reaction (PCR) analysis that had the capability of distinguishing between wild-type and vaccine VZV strains. A specimen was also obtained for virus culture if a local virology laboratory was available to the study site. Confirmation of evaluable cases of HZ was determined according to a hierarchical algorithm that first considered the result of the PCR assay and the virus culture (Figure 2). These assays were performed independently of clinical adjudication. Final determinations on cases that were not resolved by the laboratory results were made according to the consensus decision of the CEC.

Figure 2

Flow Chart of Evaluable HZ Case Determination for the Modified Intention-to-Treat
(MITT) Population
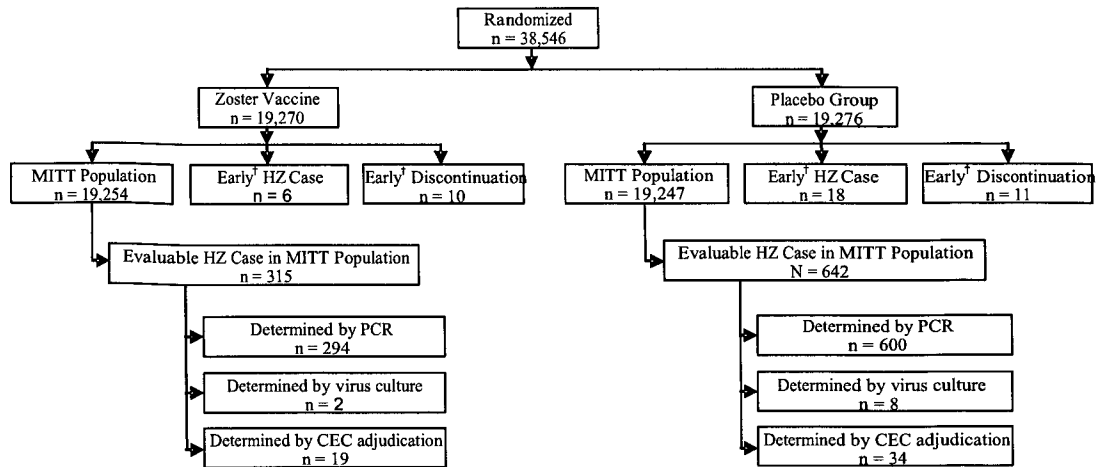
†Early = Within 30 days of vaccination.
Only the number of evaluable HZ cases determined by PCR or virus culture or CEC adjudication within the
respective vaccination group in the MITT population was presented here.

The original protocol defined PHN as any clinically significant pain (score ≥3 on a scale
of 0 to 10, in which 0 = no pain and 10 = worst possible pain) present more than 30 days
after rash onset. During the conduct of the study, a protocol amendment altered the
primary cutoff for PHN to 90 days after HZ rash onset, while retaining other time points
(30, 60, 120, and 182 days after HZ rash onset) as supportive cutoffs. This longer
interval from HZ rash onset to PHN is a more conservative definition of chronic pain,
including PHN, that is currently accepted by experts.

As outlined in Section 2.1, the study population was heterogeneous with respect to
gender, as well as underlying medical conditions and concomitant therapies (Table 2).
The population was predominantly white (36,774 subjects [95.4%]), but the population
studied also included 1765 (4.6%) non-white subjects (7 subjects did not report their
race).

Table 2

Summary of Baseline Characteristics for All Shingles Prevention Study Participants

	ZOSTAVAX™ (N=19270)		Placebo (N=19276)		Total (N=38546)	
	n	(%)	n	(%)	n	(%)
Gender						
Male	11403	59.2	11357	58.9	22760	59.0
Female	7867	40.8	7919	41.1	15786	41.0
Age (in years)						
59	0	0.0	1	0.0	1	0.0
60 to 64	5219	27.1	5202	27.0	10421	27.0
65 to 69	5159	26.8	5166	26.8	10325	26.8
70 to 74	4547	23.6	4568	23.7	9115	23.6
75 to 79	3082	16.0	3004	15.6	6086	15.8
80 to 84	1063	5.5	1100	5.7	2163	5.6
85 to 89	181	0.9	210	1.1	391	1.0
90 to 94	17	0.1	25	0.1	42	0.1
≥ 95	2	0.0	0	0.0	2	0.0
Mean	69.4		69.4		69.4	
SD	6.3		6.3		6.3	
Median	69		69		69	
Range	60-99		59-94		59-99	
Race						
Black	395	2.0	420	2.2	815	2.1
Hispanic	265	1.4	248	1.3	513	1.3
White	18393	95.4	18381	95.4	36774	95.4
Other	214	1.1	223	1.2	437	1.1
Unknown	3	0.0	4	0.0	7	0.0
Note: One subject (AN 5210901) was enrolled outside of protocol specified age range.						

Section 3.2 presents immunogenicity data from 7 clinical studies. In particular, the CMI Substudy of the Shingles Prevention Study, which was designed to assess immunogenicity among a subset of subjects who were followed for efficacy, is summarized in Section 3.2.

3.1 Analysis of Clinical Efficacy

The primary efficacy analyses in the Shingles Prevention Study were performed on a modified-intention-to-treat (MITT) population, which did not include subjects who had less than 30 days of follow-up or who developed HZ in the first 30 days following vaccination. Very similar results were provided by analyses on the full intention-to-treat (ITT) population. The decision to use the 30-day cutoff was based on the following reasons: (1) reactivation of latent VZV and the subsequent replication of virus in the sensory ganglion (the stage at which VZV-specific immune responses are thought to

modulate the development of HZ and PHN) precedes the development of clinically evident HZ by a week or more, so that cases of HZ occurring within 30 days of vaccination may have been in development prior to vaccination; (2) the VZV-specific immune response to the vaccine is not likely to be fully developed until sometime after vaccination; and (3) cases of HZ cases may be confounded with vaccine-induced rashes. In other words, most rashes during the first 30 days after vaccination may not be HZ, but may be vaccine-related or unrelated to VZV (e.g., localized folliculitis, contact dermatitis).

As designed by the VA CSP, the protocol had a single primary endpoint (HZ pain BOI), a single secondary endpoint (incidence of PHN), and a large number of tertiary and exploratory endpoints. However, at the outset of the study, HZ pain BOI and incidence of PHN were considered co-primary for purposes of the license application, such that success on either endpoint, with appropriate multiplicity adjustment, would represent a successful study.

During the conduct of the trial, it was learned for the first time that vaccination might reduce the frequency of HZ [59]. At that point, the incidence of HZ, the duration of clinically significant HZ pain, and the substantial interference of activities of daily living (ADLI) due to HZ were elevated to secondary endpoints, accompanied by prespecified success criteria and strategies for multiplicity adjustment. A plan was developed to evaluate all of these endpoints in a hierarchical (3-tiered) sequence, using the Hochberg step-up procedure for multiplicity adjustment within each tier. Progression to hypothesis testing in the next tier was conditional on success in the previous tiers.

Section 3.1.1 through Section 3.1.4 which follow, briefly describe the 3 tiers of the statistical analysis plan, along with the results for each of the key efficacy endpoints and the multiplicity adjustment. Figure 3 provides a visual representation of the design and implementation of the 3-tiered statistical testing procedure, including the prespecified criteria for success and observed results at each step.

Figure 3

Assessment of the Success of the Shingles Prevention Study Based on a 3-Tiered
Multiplicity Adjustment Strategy (MITT Population)

Steps for Assessing Study Success or Failure

Tier-1 Testing at α=0.05[†]

Point Estimate of
VE_{BOI} = 61.1%
95% CI = (51.1%, 69.1%)

Success for HZ BOI demonstrated
at α = 0.05 as both VE_{BOI} >47% and
lower bound of the 95% CI >25%

Point Estimate of
VE_{PHN} = 66.5%
95% CI = (47.5%, 79.2%)

Success for Incidence of PHN demonstrated
at α= 0.05 as both VE_{PHN} >62% and
lower bound of the 95% CI >25%

Tier-2 Testing at α=0.05[†]

Point Estimate of
VE_{HZ} = 51.3%
95% CI = (44.2%, 57.6%)

Success for Incidence of HZ demonstrated
at α = 0.05 as lower bound of the 95% CI
>25%

Median Duration of Clinically Significant HZ
Pain: 20 days vs. 22 days
Log-rank p-value<0.001 based on the MITT
Population

Success for Duration of HZ Pain demonstrated
at α= 0.05 (p-value<0.001)

Tier-3 Testing at α=0.05

Point Estimate of $VE_{SADLI:HZ}$=8.2% (95% CI = [-9.4%, 22.9%])
Did not reach statistical significance (p-value=0.341).

[†] Hypothesis testing at this tier was performed using the Hochberg step-up procedure to control the type I
error rate at the two-sided 0.05 significance level.
The MITT population includes all subjects randomized in the study who were followed for at least 30 days
and did not develop evaluable cases of HZ (per the hierarchical algorithm specified in Protocol
Amendment 6) within the first 30 days after vaccination.
PHN cases are defined as any HZ-associated pain rated as ≥3 (on a 0 to 10 scale) persisting or appearing
more than 90 days after the HZ rash onset.
$VE_{SADLI:HZ}$ = Vaccine efficacy for substantial ADLI above-and-beyond VE_{HZ}

3.1.1   Efficacy Based on Incidence of Herpes Zoster

The incidence of HZ was a key efficacy endpoint in the study. Vaccine efficacy for HZ (VE_{HZ}) was defined as the relative reduction in the HZ incidence rate in the ZOSTAVAX™ group compared with the placebo group. Compared with placebo, ZOSTAVAX™ reduced the incidence of HZ (315 [5.4/1000 person-years] evaluable HZ cases in the ZOSTAVAX™ group versus 642 [11.1/1000 person-years] in the placebo group). The estimated VE_{HZ} was 51.3% (95% CI = [44.2%, 57.6%]), which exceeded the prespecified success criterion (Table 3).

The reduction in HZ incidence was 63.9% (95% CI = [55.5%, 70.9%]) in subjects 60 to 69 years of age and 37.6% (95% CI = [25.0%, 48.1%]) in subjects ≥70 years of age (Table 4). For this secondary endpoint, the test of treatment-by-age-group interaction was statistically significant. However, even within the older subpopulation, the lower bound of the 95% CI met the 25% criterion for success, and so remained statistically significant. These data also suggest that with vaccination beginning at 50 years of age, the reduction in HZ incidence should be at least as great in the 50-to-59 age range as in the 60-to-69 age range.

Table 3

Statistical Analysis of Incidence of Evaluable HZ Cases
(MITT Cases)
(The Shingles Prevention Study)

ZOSTAVAX™ (N = 19270)				Placebo (N = 19276)				Vaccine Efficacy With Respect to HZ
n	m	Total Follow-Up Time (Person-Years)	Estimated Incidence Rate of HZ† (Per 1000 Person-Years)	n	m	Total Follow-Up Time (Person-Years)	Estimated Incidence Rate of HZ† (Per 1000 Person-Years)	Point Estimate (95% CI)‡
315	19254	58203	5.415	642	19247	57736	11.119	0.513 (0.442, 0.576)

p-Value for testing the vaccine efficacy for HZ being >25% was <0.001 and >0% was <0.001; p-value for testing treatment-by-age-group interaction in vaccine efficacy for HZ was <0.001.

† Weighted average of the observed incidence rate stratified by age group (60 to 69 years, ≥70 years of age) with Mantel-Haenszel weights associated with the total follow-up time in each age group.

‡ Calculated as 1 minus the ratio of the estimated incidence rates of HZ in the ZOSTAVAX™ group and placebo group. The CI is constructed based on the exact conditional procedure stratified by age group.

n = Number of evaluable HZ cases in the MITT population.

m = Number of subjects in the MITT population.

Table 4

Statistical Analysis of Incidence of Evaluable HZ Cases by Age Group
(MITT Population)
(The Shingles Prevention Study)

Age Group	ZOSTAVAX™ (N = 19270)				Placebo (N = 19276)				Vaccine Efficacy With Respect to HZ
	n	m	Total Follow-Up Time (Person-Years)	Estimated Incidence Rate of HZ (Per 1000 Person-Years)	n	m	Total Follow-Up Time (Person-Years)	Estimated Incidence Rate of HZ (Per 1000 Person-Years)	Point Estimate (95% CI)[†]
(Years)									
60 to 69	122	10370	31323	3.895	334	10356	30953	10.791	0.639 (0.555, 0.709)
≥70	193	8884	26881	7.180	308	8891	26783	11.500	0.376 (0.250, 0.481)

[†] Calculated as 1 minus the ratio of the estimated incidence rates of HZ in ZOSTAVAX™ group and the placebo group. The CI is constructed based on the exact conditional procedure.

n = Number of evaluable HZ cases in the respective age groups of the MITT population.

m = Number of subjects in the respective age groups of the MITT population.

3.1.2 Efficacy Based on Incidence of Postherpetic Neuralgia

Vaccine efficacy against PHN (VE_{PHN}) was defined as the relative reduction in PHN incidence rate in the ZOSTAVAX™ group compared with the placebo group. PHN was defined as HZ-associated pain rated as ≥ 3 (on a 0 to 10 scale) persisting or appearing more than 90 days after the onset of the HZ rash. Compared with placebo, ZOSTAVAX™ reduced the incidence of PHN (27 PHN cases in the ZOSTAVAX™ group versus 80 PHN cases in the placebo group). The estimated VE_{PHN} was 66.5% (95% CI = [47.5%, 79.2%]), which met the prespecified success criteria ($VE_{PHN} \geq 62\%$; lower bound of the 95% CI > 25%) for this endpoint (Table 5). Statistical analyses using alternative time cutoffs (30, 60, 120, and 182 days after rash onset) showed very consistent vaccine effects, based on different PHN definitions (Table 6). Using 120 days after rash onset, which is another widely accepted time point for defining PHN, VE_{PHN} was 68.7% (95% CI = [45.2%, 83.0%]).

Table 5

Statistical Analysis of the Incidence of PHN
(MITT Population)
(The Shingles Prevention Study)

ZOSTAVAX™ (N = 19270)				Placebo (N = 19276)				Vaccine Efficacy With Respect to PHN
n	m	Total Follow-Up Time (Person-Years)	Estimated Incidence Rate of PHN† (Per 1000 Person-Years)	n	m	Total Follow-Up Time (Person-Years)	Estimated Incidence 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; p-value for testing the vaccine efficacy for PHN >0% was <0.001; p-value for testing treatment-by-age-group-interaction in vaccine efficacy for PHN was >0.999.

† Weighted average of the observed incidence rate stratified by age group (60 to 69, ≥70 years of age) with Mantel-Haenszel weights associated with the total follow-up time in each age group.

‡ Calculated as 1 minus the ratio of the estimated incidence rates of PHN in the vaccine group and placebo group. The CI is constructed based on the exact conditional procedure stratified by age group.

n = Number of PHN cases (defined as any HZ-associated pain ≥3 [on a 0 to 10 scale] persisting or appearing ≥90 days after the HZ rash onset) in the MITT population.

m = Number of subjects in the MITT population.

Table 6

Statistical Analysis of Incidence of PHN Using Alternative PHN Definitions
(MITT Population)
(The Shingles Prevention Study)

PHN Defined by Cutoff Day (After Rash Onset)	ZOSTAVAX™ (N = 19270)				Placebo (N = 19276)				Vaccine Efficacy With Respect to PHN
	n	m	Total Follow-Up Time (Person-Years)	Estimated Incidence Rate of PHN† (Per 1000 Person-Years)	n	m	Total Follow-Up Time (Person-Years)	Estimated Incidence Rate of PHN† (Per 1000 Person-Years)	Point Estimate (95% CI)‡
30	81	19254	58203	1.393	196	19247	57736	3.393	0.589 (0.466, 0.687)
60	45	19254	58203	0.774	113	19247	57736	1.956	0.604 (0.436, 0.726)
90	27	19254	58203	0.464	80	19247	57736	1.384	0.665 (0.475, 0.792)
120	17	19254	58203	0.292	54	19247	57736	0.934	0.687 (0.452, 0.830)
182	9	19254	58203	0.155	33	19247	57736	0.571	0.729 (0.421, 0.886)

† Weighted average of the observed incidence rate stratified by age group (60 to 69, ≥70 years of age) with Mantel-Haenszel weights associated with the total follow-up time in each age group.
‡ Calculated as 1 minus the ratio of the estimated incidence rates of PHN in the vaccine group and placebo group. The CI is constructed based on the exact conditional procedure stratified by age group.
PHN for co-primary endpoint is defined as any HZ-associated pain rated ≥3 (on a 0 to 10 scale) persisting or appearing more than 90 days after the HZ rash onset.
Alternative PHN definitions are pain ≥3 persisting or appearing more than 30, 60, 120, or 182 days after HZ rash onset.
n = Number of PHN cases (defined as any HZ-associated pain ≥3 [on a 0 to 10 scale] persisting or appearing more than the respective cutoff days after the HZ rash onset) in the MITT population.
m = Number of subjects in the MITT population.

3.1.3   Efficacy Based on Herpes Zoster Burden of Illness

The primary efficacy analysis of HZ-associated pain compared the HZ pain BOI score in the ZOSTAVAX™ group with that in the placebo group. The HZ pain BOI score was a composite endpoint incorporating the incidence, severity, and duration of HZ pain. As such, HZ BOI captures combined acute and chronic HZ-associated pain. For a given group of subjects (e.g., all placebo recipients), the HZ pain BOI score was the sum of the HZ pain severity-by-duration scores for each individual subject, divided by the number of subjects in that group. For an individual subject who developed HZ, the severity-by-duration score of HZ pain was defined as the area under the worst pain response (rated on a 0-to-10 scale) versus time curve (AUC) during the 6-month period following HZ rash onset. For example, a subject experiencing a worst pain score of 10 for 30 days and worst pain scores of 0 for the remainder of the 6-month follow-up period would have a severity-by-duration score of 300, whereas a subject experiencing a worst pain score of 5 for 40 days and 0 for the remaining days would have a severity-by-duration score of 200. For subjects who did not develop HZ during the study, the individual HZ BOI score was defined as zero. This individual score was also referred to as the severity-of-illness score for an individual subject. For a group of subjects (e.g., all placebo recipients), the HZ pain BOI score can be calculated as the proportion of subjects who developed HZ, multiplied by the mean severity-by-duration score among subjects who developed HZ. A "worst pain" score was obtained using the validated ZBPI questionnaire. These scores were used to calculate a total "severity-by-duration" score during 6 months of follow-up after onset of HZ rash. In the validation study, the ZBPI questionnaire demonstrated reliability and validity as a measure of HZ pain and discomfort, with a worst pain score ≥ 3 being associated with an impact on quality of life and ability to carry out ADL [60].

The statistical analysis on the co-primary endpoint of HZ pain BOI indicated that compared with placebo, ZOSTAVAX™ significantly reduced the BOI related to HZ pain. The estimated vaccine efficacy for BOI (VE_{BOI}) was 61.1% (95% CI = [51.1%, 69.1%]), which met the prespecified success criteria ($VE_{BOI} \geq 47\%$, lower bound of the 95% CI >25%) for this endpoint (Table 7).

Table 7

Statistical Analysis of HZ Pain BOI Efficacy Based on the Protocol-Defined AUC Scale[†]
Over 6 Months of Follow-Up After HZ Rash Onset
(MITT Population)
(The Shingles Prevention Study)

	ZOSTAVAX™ (N = 19270)			Placebo (N = 19276)			Vaccine Efficacy for HZ Pain BOI
			Total Follow-Up Time (Person-Years)	Estimated HZ Pain BOI[‡]			
n	m	Total Follow-Up Time (Person-Years)	Estimated HZ Pain BOI[‡]	n	m		Point Estimate (95% CI)[§]
315	19254	58203	2.208	642	19247	57736	5.682	0.611 (0.511, 0.691)

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-group-interaction in vaccine efficacy for BOI was 0.266 .

[†] Protocol-defined AUC: (1) incorporates patient-reported data on HZ pain between rash onset and the first patient interview collected on the Initial Zoster Impact Questionnaire (IZIQ); (2) excludes pain scores <3 that occur on 2 or more consecutive visits more than 30 days after rash onset; and (3) includes recurrent pain with score ≥3 beyond 30 days after HZ rash onset.

[‡] Weighted average of the observed HZ pain BOI stratified by age group (60 to 69, ≥70 years of age) with weights proportional to the total follow-up time in each age group.

[§] Calculated as a weighted average of the observed vaccine efficacy stratified by age group with weights proportional to the total follow-up time in each age group. The CI is constructed based on the large sample approximation under the fixed-number-of-events design.

n = Number of evaluable HZ cases in the MITT population.

m = Number of subjects in the MITT population.

As shown in Figure 3, success was demonstrated in both the HZ pain BOI and PHN incidence endpoints at the 2-sided 0.05 significance level. Therefore, the Shingles Prevention Study was declared a success, having successfully met the prespecified criteria for success on both of its co-primary endpoints. Indeed, for both endpoints, the lower bounds of the 95% CIs were much higher than the criterion of 25% that had been established in the protocol and Data Analysis Plan.

Perhaps the most compelling BOI-related result comes from the severity-by-duration analysis. Supportive analyses showed that among subjects who developed HZ, mean severity-by-duration scores were lower in the ZOSTAVAX™ group than in the placebo group (141.2 versus 180.5, p-value = 0.008). At higher severity-by-duration scores, the differences between groups were even more dramatic. For example, the group with severity-by-duration scores >600 (e.g., as would be achieved with a maximal score of 10 for >60 days) included only 11 ZOSTAVAX™ recipients, compared with 40 placebo recipients, a reduction of 72.6% (95% CI = [45.7%, 87.3%]). Also, among subjects who developed PHN (i.e., pain present at least 90 days after HZ rash onset), the mean severity-by-duration scores through the end of HZ follow-up were 57% lower for the ZOSTAVAX™ group than for the placebo group (346.7 versus 805.2; p-value = 0.016). These analyses demonstrate the value of the vaccine at reducing the "tail" in the distribution at the highest severity-by-duration scores (Figure 4).

Figure 4

Histogram of Severity-by-Duration Score (AUC) of HZ Pain Calculated Using
the Protocol-Defined AUC Scale Over the 6-Month HZ Follow-Up
Among Evaluable HZ Cases by Vaccination Group
(MITT Population)
(Shingles Prevention Study)

HZ-Associated Pain Severity-by-Duration Score (AUC)
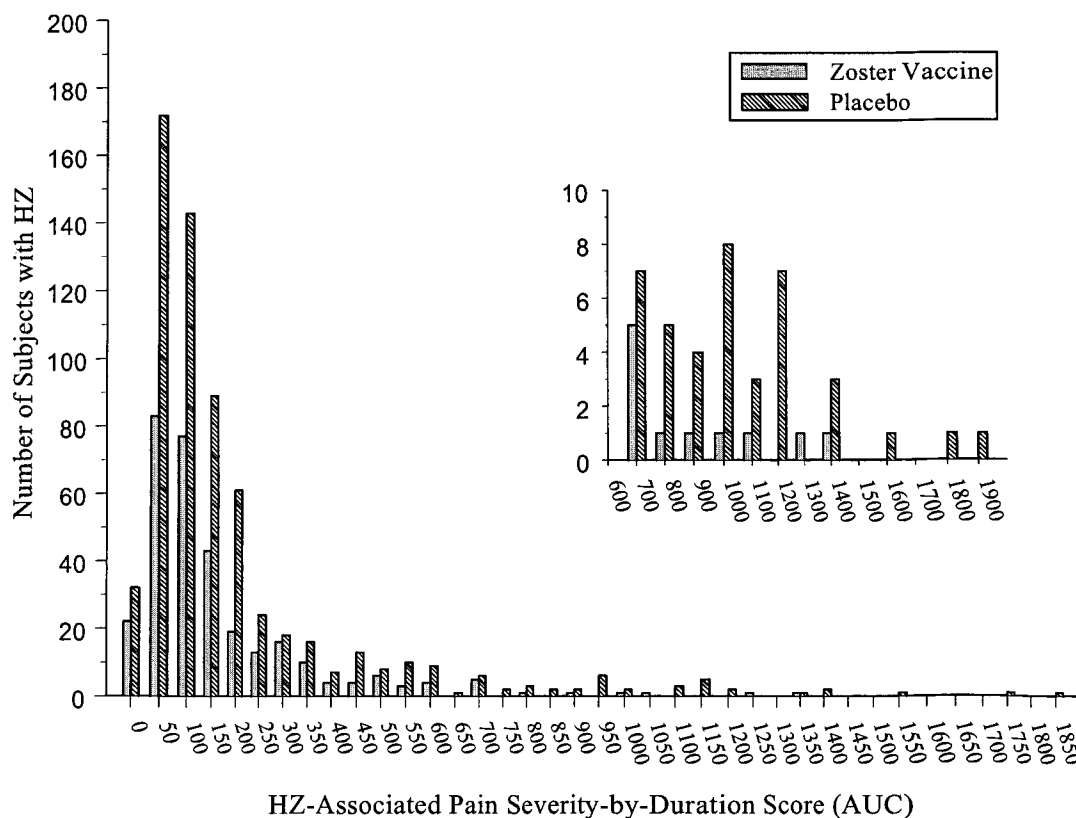
The first bar in the histogram represents the number of subjects with zero AUC score.
Forty-two (42) subjects in the zoster vaccine group and 103 subjects in the placebo group had
severity-by-duration score >300. Eleven (11) subjects in the zoster vaccine group and 40 subjects
in the placebo group had severity-by-duration score >600.
N = Number of subjects randomized.
n = Number of evaluable HZ cases.

For both age cohorts, the observed HZ pain BOI and the incidence rate of PHN were both much lower in the ZOSTAVAX™ group than in the placebo group, and the vaccine efficacy was similar across the 2 age categories. Thus, for both of the study's co-primary endpoints, age did not have an impact on the protection afforded by the vaccine. However, data summaries and analyses suggested that, independent of vaccination group, the observed HZ pain BOI and incidence rate of PHN were substantially higher in subjects ≥70 years of age than in subjects 60 to 69 years of age.

3.1.4 Efficacy Based on Duration of Zoster-Associated Pain and Interference With Activities-of-Daily-Living

Another secondary efficacy endpoint in the second tier of the statistical analysis regarded the vaccine effect on the duration of clinically significant HZ pain (defined as the number of days between the first day after HZ 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 6-month follow-up period) among evaluable HZ cases. Compared with placebo, ZOSTAVAX™ reduced the duration of clinically significant pain associated with HZ (median in the ZOSTAVAX™ and placebo groups: 20 days versus 22 days; p-value<0.001 in the MITT population, p-value=0.041 among evaluable HZ cases). Thus, as shown in Figure 3, success was demonstrated in both the HZ incidence and duration of clinically significant HZ pain endpoints at the 2-sided 0.05 significance level.

To asses the effect of ZOSTVAX™ on interference with ADL, which constituted the third tier of the statistical analysis for efficacy, the following analyses were performed:

1) ADL based on an AUC scale over 6 months of follow-up after HZ rash onset <u>among all subjects</u> in the MITT population (analogous to the pain BOI methodology)

2) Severity-by-duration scores of a combined ADL score from the ZBPI <u>among evaluable HZ cases</u>

3) Vaccine efficacy for <u>substantial</u> (moderate to severe) interference with ADL <u>above-and-beyond the vaccine efficacy for incidence of HZ</u> (a prespecified endpoint)

The relative reduction in the severity-by-duration measure of combined ADL score (the average of 7 ADL questions on the ZBPI, each measured on a 0 to 10 scale) was estimated using the same method as for the primary efficacy analysis of HZ pain BOI with stratification by age group. ZOSTAVAX™ reduces the pain interference with ADL by 66.2% (95% CI: 55.4%, 74.4%), when compared with placebo. A large proportion of this reduction may have resulted from the reduction of HZ incidence in the vaccine group.

Among subjects in the MITT population who developed HZ, ZOSTAVAX™ was associated with a 31% reduction in the combined ADL severity-by-duration score over the 6-month follow-up period after HZ rash onset (57.0 for ZOSTAVAX™, 83.0 for placebo; p=0.002).

Vaccine efficacy for substantial ADLI above-and-beyond vaccine efficacy for HZ ($VE_{SADLI:HZ}$), based on a combined ADL score, was the final prespecified efficacy hypothesis, in the third tier of the analysis strategy. Substantial ADLI was defined as a combined ADLI score ≥ 2 for ≥ 7 days. Before removing the effect of ZOSTAVAX™ on HZ incidence, compared with placebo, there was a 55.3% reduction in substantial interference with ADLI. Compared with placebo, ZOSTAVAX™ resulted in an 8.2% reduction in the risk of having substantial ADLI beyond the vaccine effect on HZ incidence. The hypothesis testing on this endpoint was not statistically significant (p-value=0.341), so efficacy on this last prespecified endpoint was not demonstrated. In a supporting analysis using a more stringent definition of "substantial", a combined ADLI score ≥ 3 for ≥ 7 days, the ZOSTAVAX™ group had a 21.3% (95% CI = [0.5%, 37.7%]) reduction, compared with the placebo group, in the risk of having substantial ADLI beyond the reduction in HZ (p-value=0.045).

3.1.5   Effect of ZOSTAVAX™ on Complications of HZ

A summary of HZ complications that occurred in at least one subject in either vaccination group is provided in Table 8. Of note, consistent with the observed VEHZ of 51%, the complications of HZ displayed in Table 8 were also reduced by approximately half among subjects who received ZOSTAVAX™. The most frequently reported complications ($\geq 10\%$ in at least one vaccination group) were prodromal pain, acute pain, any pain after 30 days after rash onset, and allodynia. Other complications that were reported with frequencies of $\geq 1\%$ in at least one vaccination group were disseminated rash, scarring, motor neuron palsies, sensory loss, ptosis, and vision impairment. In terms of life-threatening complications, pneumonitis was reported in 0.5% of the cases in the placebo group; cerebral dysfunction was reported in one subject in the placebo group; and meningoencephalitis was reported in one subject in the vaccine group.

Table 8

Summary of HZ Complications Among Evaluable Cases of HZ
(ITT Population)

	Zoster Vaccine (N = 19270)		Placebo (N = 19276)	
	n/m	(%)	n/m	(%)
Number of evaluable HZ cases	321		660	
Cutaneous	**41/321**	**(12.8)**	**118/659**	**(17.9)**
Dissemination	5/321	(1.6)	11/659	(1.7)
Scarring	24/321	(7.5)	57/659	(8.6)
Bacterial Superinfection	3/321	(0.9)	7/659	(1.1)
Other	15/319	(4.7)	56/659	(8.5)
Neurologic	**298/321**	**(92.8)**	**634/659**	**(96.2)**
Prodromal Pain	190/321	(59.2)	425/659	(64.5)
Acute Pain	289/321	(90.0)	617/659	(93.6)
Any Pain After 30 days after rash onset	135/321	(42.1)	278/659	(42.2)
Allodynia	135/321	(42.1)	310/659	(47.0)
Peripheral Nerve Palsies (motor)	5/321	(1.6)	12/659	(1.8)
Peripheral Nerve Palsies (autonomic)	0/321	(0.0)	1/659	(0.2)
Sensory Loss	7/321	(2.2)	12/659	(1.8)
Hearing Loss	0/321	(0.0)	6/659	(0.9)
Tinnitus	0/321	(0.0)	4/659	(0.6)
Vestibular Dysfunction	1/321	(0.3)	2/659	(0.3)
Other Cranial Neuropathy	1/321	(0.3)	5/659	(0.8)
Cerebral Dysfunction	0/321	(0.0)	1/659	(0.2)
Meningoencephalitis	1/321	(0.3)	0/659	(0.0)
Other	19/321	(5.9)	49/658	(7.4)
Ocular Involvement	**14/321**	**(4.4)**	**40/659**	**(6.1)**
Ptosis	2/321	(0.6)	9/659	(1.4)
Lid Deformity	1/321	(0.3)	3/659	(0.5)
Conjunctivitis	3/321	(0.9)	5/659	(0.8)
Corneal Disease	0/321	(0.0)	6/659	(0.9)
Scleritis	0/321	(0.0)	1/659	(0.2)
Iritis	1/321	(0.3)	1/659	(0.2)
Uveitis	0/321	(0.0)	2/659	(0.3)
Glaucoma	0/321	(0.0)	2/659	(0.3)
Impaired Vision	2/321	(0.6)	9/659	(1.4)
Other	8/319	(2.5)	27/658	(4.1)
Sacral Dermatome Involvement	**6/321**	**(1.9)**	**25/659**	**(3.8)**
Urinary Retention	1/321	(0.3)	3/659	(0.5)
Other	6/321	(1.9)	23/652	(3.5)
Visceral Complications	**9/321**	**(2.8)**	**29/659**	**(4.4)**
Pneumonitis	0/321	(0.0)	3/659	(0.5)
Hepatitis	0/321	(0.0)	1/659	(0.2)
Gastritis	0/321	(0.0)	1/659	(0.2)
Arthritis	1/321	(0.3)	2/659	(0.3)
Other	8/321	(2.5)	25/651	(3.8)
m = Number of subjects who responded to the question in the respective category. n = Number of subjects with an incidence in the respective category.				

3.1.6   Duration of Efficacy

Subjects enrolled in the Shingles Prevention Study were followed for a mean of just over 3 years; no subjects were followed for as long as 5 years. A number of analyses on duration of effect were performed. These analyses found that the efficacy decreased somewhat very early after vaccination, but stabilized thereafter. Based on the available data, the vaccine has demonstrated continuing efficacy for incidence of HZ through Year 4 postvaccination (Figure 5). A similar pattern of continuing efficacy is seen for incidence of PHN (Figure 6), although the numbers of PHN cases is small, especially in the later time periods. No definitive conclusion can be made about vaccine efficacy beyond Year 4 for either HZ incidence or PHN incidence, because of the small number of subjects who had follow-up beyond 4 years postvaccination. Data on the persistence of efficacy for 5 years or longer will accrue in a long-term persistence study, which is beginning in the fall of 2005 at 12 of the 22 Shingles Prevention Study sites.

Figure 5

Nonparametric Estimate of Vaccine Efficacy for the Incidence of HZ with 95%
Confidence Intervals Over Time
(MITT Population)
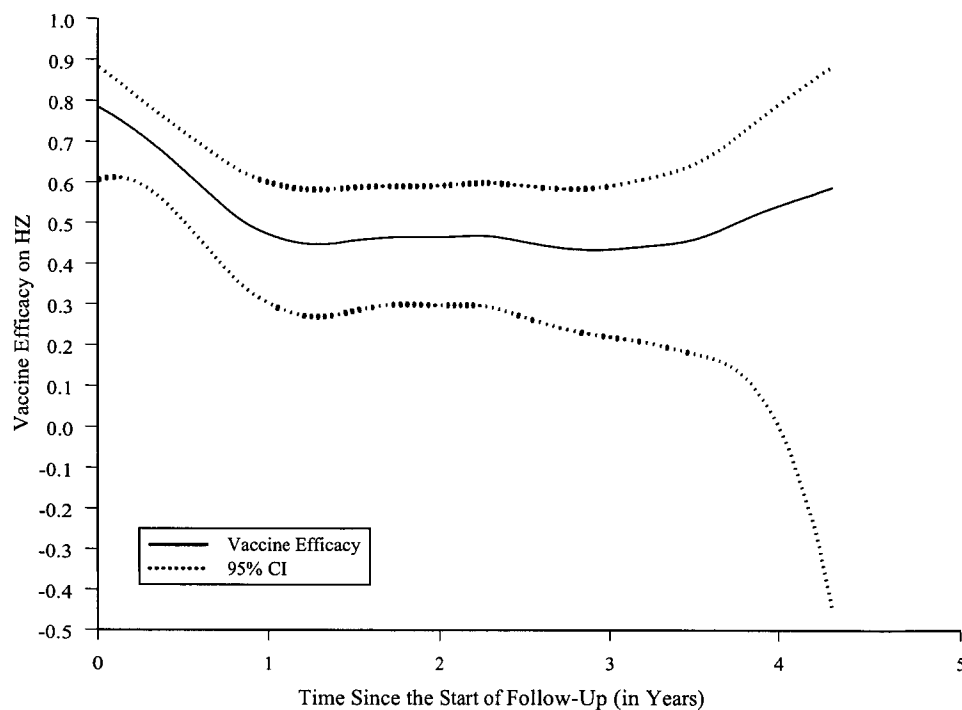
Figure 6

Nonparametric Estimate of Vaccine Efficacy for the Incidence of PHN with 95%
Confidence Intervals Over Time
(MITT Population)
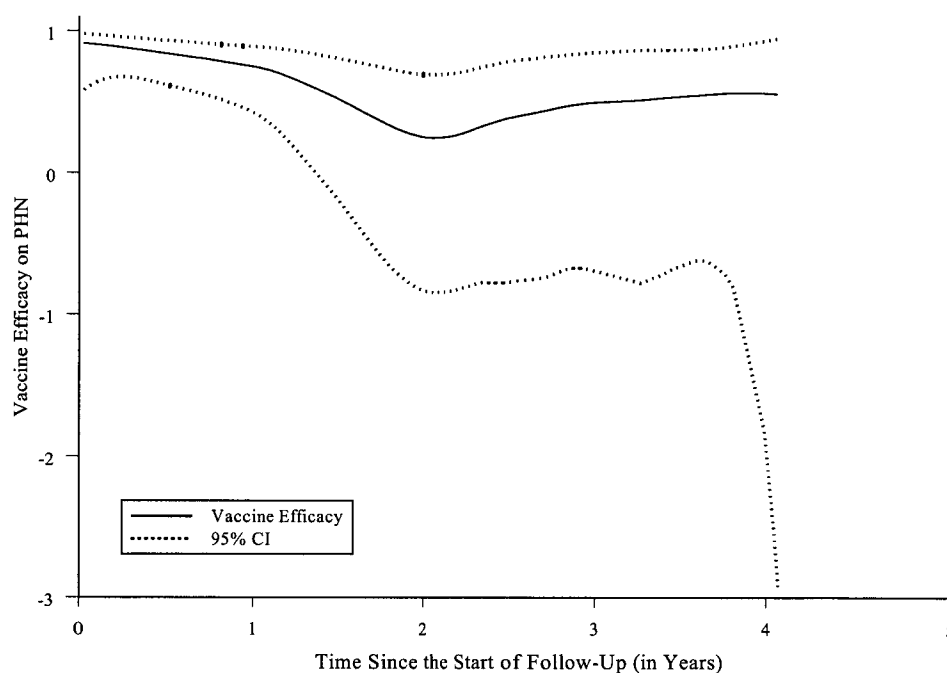
3.1.7 Discussion of Efficacy Results

In the Shingles Prevention Study, a single dose of ZOSTAVAX™ proved to be highly efficacious in preventing HZ and PHN, in reducing the HZ pain BOI, and in shortening the duration of clinically significant HZ pain. Because a large majority of the vaccine doses were administered near the projected expiry potency, efficacy can be inferred throughout the range of potencies that are proposed during the vaccine's shelf life. The magnitude of the reduction for each of the endpoints is clinically important, and the evidence for HZ pain BOI and PHN incidence is particularly compelling, because the protocol permitted administration of antivirals and analgesic medications according to physician preference and the current standard of care. Both of these therapeutic interventions could have had an effect across vaccination groups by ameliorating pain, thereby biasing toward the null for both of the co-primary endpoints. Thus, the vaccine was highly efficacious, above-and-beyond the benefits associated with standard therapy, thereby showing a significant impact beyond the current state-of-the-art treatment approach. On this basis, the efficacy data strongly support the proposed indications.

The primary efficacy analyses were performed on an MITT population (Table 9), which excluded subjects who had less than 30 days of follow-up or who developed HZ in the first 30 days following vaccination. The results of supportive analyses performed on the ITT population were essentially unchanged compared with those in the MITT population.

Table 9

Summary of Vaccine Efficacy in the Shingles Prevention Study

	Point Estimate (MITT Analysis)	Point Estimate (ITT Analysis)
VE_{HZ}	51.3%	51.7%
VE_{PHN}	66.5%	65.2%
VE_{BOI}	61.1%	60.4%
VE_{ADLI}	66.2%	Not Performed

The endpoints evaluated in the Shingles Prevention Study focused on clinically relevant issues. The HZ pain BOI co-primary endpoint was a composite endpoint, developed for use in vaccine efficacy studies, that was sensitive to the incidence, severity, and duration of pain [61]. The ZBPI questionnaire, which had been adapted from a generally accepted tool that was originally used in the setting of cancer pain [62], underwent a thorough validation before being implemented in the Shingles Prevention Study [60]. A pilot study and a validation study found that worst pain scores of 1 or 2 were associated with minimal disruption in ADL, whereas significant ADL interference was associated with scores of 3 of higher [63; 60]. Therefore, a pain score level of 3 was chosen as the threshold for the pain endpoints. The study results demonstrated that the HZ pain BOI was significantly reduced. At higher severity-by-duration scores, the differences between groups were even more dramatic. These analyses highlight the impact of the vaccine at reducing pain at the severe end of the spectrum, among subjects with the highest severity-by-duration scores, where HZ causes its most serious human suffering.

In addition to the very strong efficacy results with the PHN 90 day primary time point, supportive analyses using several alternative time points corroborated the primary result. No matter how one delineates the time cutoff defining PHN, the vaccine was highly efficacious. As one might have expected, with each successively later time point, the point estimate for VE_{PHN} increased, to as high as 72.9% at 182 days after HZ rash onset, while the 95% CI widened, due to smaller numbers of subjects with longer-term pain. Overall, the lower bounds of the 95% CI were relatively stable across the time points evaluated. The treatment-by-age interaction indicated no statistical difference in efficacy across the 2 age cohorts.

The estimated VE_{HZ} was particularly high in the cohort of subjects 60 to 69 years of age, which is an important benchmark for the potential utility of the vaccine in those 50 to 59 years of age, who have an appreciable incidence of HZ, but less frequently develop PHN than older persons. The estimated VE_{HZ} in the subjects ≥70 years of age, although somewhat lower than in the younger subjects, was still appreciable (37.6%; 95% CI = [25.0%, 48.1%]).

The high degree of protection from HZ demonstrated in this study represents a clinically important reduction in disease incidence, even in the ≥70-year age group. The age effect on reduction in HZ incidence is an interesting biological observation. It may be that vaccine efficacy is achieved along a biological continuum--although it more often prevents HZ altogether in younger subjects, the vaccine still provides statistically significant protection against HZ in subjects ≥70 years of age, and also ameliorates significantly the pain associated with HZ in the older subpopulation. This subtle biological shift in the characteristics of the performance of the vaccine may be a function of a more vigorous immune response in the younger cohort. Nevertheless, as it did for HZ pain BOI and PHN incidence, the vaccine provided statistically significant protection against HZ in both age cohorts.

The Shingles Prevention Study enrolled subjects 60 years of age and older, with age stratification (60 to 69 years, ≥70 years). In addition to assuring a representative sample for purposes of the safety and immunogenicity evaluation, this decision took into consideration the age-related increase in the incidence of HZ and PHN, and was designed to accrue the requisite number of evaluable HZ and PHN cases within the time frame established for the study. However, given the very strong evidence for efficacy against HZ in particular, especially among subjects in the younger age stratum, the information in Section III.1 support the use of ZOSTAVAX™ beginning at 50 years of age. Noteworthy in published age-specific summaries of HZ incidence is the substantial increase in incidence beginning at 50 years of age. For example, Figure 1 shows an approximate doubling in incidence from age 40 to 49 years, to age 50 to 59 years. Thus, rather than manifesting a gradual increase in incidence with age, there appears to be an inflection point at 50 years of age. Combining this observation of age-specific incidence with the age-stratified HZ efficacy in the pivotal study, the benefit of ZOSTAVAX™ for individuals 50 to 59 years of age can be readily inferred. Clinical safety data for persons 50 to 59 years of age are presented in Section III.4. Additional discussion regarding the potential benefit of ZOSTAVAX™ for persons 50 to 59 years of age is presented in Section III.5.

3.2   Analysis of Immunogenicity

Evidence suggests that an intact immune response to VZV, especially VZV-specific CMI, is required to maintain VZV in its latent stage. This observation is supported by the fact that a decline in VZV-specific CMI that occurs with aging appears contemporaneously with the striking increase in frequency and severity of HZ that occurs with aging [4; 13; 15; 46].

The immunogenicity data to support licensure of ZOSTAVAX™ were derived from the Shingles Prevention Study and Protocols 001, 002, 003, 005, 007, and VARIVAX™ 049. In addition, in the Shingles Prevention Study, a subset of subjects were enrolled in a CMI Substudy (2 clinical sites—Denver and San Diego) and had blood samples collected prevaccination, at 6 weeks postvaccination, and at 1, 2, and 3 years postvaccination.

The key validated assays used to measure VZV-specific immunity in the ZOSTAVAX™ development program were the gpELISA and the VZV IFN-γ ELISPOT assay. The gpELISA had already been used for many years in the development programs for Oka/Merck varicella vaccines. The VZV IFN-γ ELISPOT assay was developed and validated because, compared with traditional CMI assays, the ELISPOT assay was viewed as a more relevant, practical, reproducible, sensitive, and specific alternative.

The key immunologic endpoints for studies conducted in this program were based on the GMTs in the gpELISA and GMCs in the VZV IFN-γ ELISPOT assay. For both assays, the ratio of the immune responses (ZOSTAVAX™ group to placebo group) at 6 weeks postvaccination and the GMFR from baseline to 6 weeks postvaccination were also evaluated.

All ZOSTAVAX™ studies evaluated the immune response at 6 weeks postvaccination. Protocol 007 also evaluated an additional time point, 2 weeks postvaccination. It was thought that in the setting of preexisting VZV-specific immunity, numerically greater immune responses might be elicited at 2 weeks postvaccination, making it easier to interpret and compare postvaccination responses. A small subset of subjects in Protocol 007 also had blood samples collected at 1 and 4 weeks postvaccination, which were assayed by VZV IFN-γ ELISPOT in order to provide an understanding of the kinetic profile of this response after vaccination.

Overall, the data presented in this section demonstrate that ZOSTAVAX™ is immunogenic.

3.2.1 Analysis of VZV-Specific Immune Responses

VZV Antibody by gpELISA

The gpELISA was performed in the Shingles Prevention Study (a subset enrolled in a CMI Substudy), Protocols 007, 002 (Postdose 1 only), 003, and VARIVAX™ Protocol 049. This assay was developed by MRL specifically to detect vaccine responses [64; 65; 66; 67]. Historically, this assay has been used to measure immune responses in the varicella vaccine development programs. The immune response detected by the gpELISA is known to be T-cell dependent. The gpELISA was also used in the ZOSTAVAX™ program as an indicator of VZV-specific immune response, and in the Shingles Prevention Study, this assay was used as a candidate immunologic correlate of protection.

ZOSTAVAX™ [Zoster vaccine live (Oka/Merck)]
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Individuals in the target population for ZOSTAVAX™ generally have high baseline VZV antibody titers in the gpELISA. Nonetheless, following a dose of ZOSTAVAX™, 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 of the Shingles Prevention Study, the estimated GMTs at 6 weeks postvaccination were 478.7 gpELISA units/mL (GMFR from baseline, 1.7) in the ZOSTAVAX™ group and 287.8 gpELISA units/mL (GMFR from baseline, 1.0) in the placebo group (Table 10). The estimated fold differences for both GMT and GMFR between the ZOSTAVAX™ and placebo groups were 1.7 (95% CI = [1.6, 1.8]). Similar trends in gpELISA responses were seen in Protocols 007, 002, and 003, and also among the 27 VZV-seropositive subjects $\geq$50 years of age in VARIVAX™ Protocol 049.

Table 10

Statistical Analysis of gpELISA Titers at 6 Weeks Postvaccination Among the CMI
Substudy Participants
(The Shingles Prevention Study)

Endpoint	ZOSTAVAX™ (N=691)		Placebo (N=704)		Fold Difference[†] [ZOSTAVAX™/ Placebo]
	n	Estimated Response[†]	n	Estimated Response[†]	(95% CI)
GMT	655	478.7	673	287.8	1.7 (1.6,1.8)
Geometric Mean Fold Rises from Day 0	655	1.7	673	1.0	1.7 (1.6,1.8)

[†] Calculated based on an analysis of covariance (ANCOVA) model, which included the natural-log-transformed gpELISA response or fold rise at 6 weeks postvaccination as the response variable, and treatment group, study site, treatment-by-site interaction term, gender, age and natural-log-transformed gpELISA response at Day 0 as independent variables. The fold differences for both GMT and Geometric Mean Fold Rise from Day 0 were the same in this setting.
The p-value for the treatment-by-study-site interaction was 0.0614. The p-value for vaccine effect was <0.001.

The gpELISA GMT at 6 weeks postvaccination was 498.7 gpELISA units/mL in subjects 60 to 69 years of age and 445.2 gpELISA units/mL in subjects $\geq$70 years of age. The corresponding fold-rise from Day 0 to 6 weeks postvaccination was 1.8 in subjects 60 to 69 years of age and 1.6 in subjects $\geq$70 years of age. Similar age-related findings were observed in other ZOSTAVAX™ clinical studies.

The clinical studies up to and including Protocol 007 generally included immunogenicity evaluation in subjects ≥60 years of age. More recent clinical studies in the ZOSTAVAX™ program have enrolled subjects beginning at 50 years of age. Among these is Protocol 010 which is investigating the comparability of safety and immunogenicity of the frozen formulation of ZOSTAVAX™ currently under regulatory review and an investigational, refrigerator-stable formulation. Enrollment in this study was stratified in a 1:2 ratio by age group (50 to 59 years of age; ≥60 years of age). An age-stratified preliminary analysis of the Protocol 010 database was recently undertaken, specifically to summarize immunogenicity (gpELISA) data among 50- to 59-year-old recipients (n = 46) and ≥60-year-old recipients (n = 68) of the frozen vaccine formulation who had provided a postvaccination blood sample prior to the prespecified cutoff date of 07-Oct-2005. The assay results were audited in the laboratory, but formal data review and the identification of protocol violators have not yet occurred. Table 11 suggests that in the subset included in the preliminary analysis, subjects 50 to 59 years of age had baseline antibody titers that were somewhat lower than did subjects ≥60 years of age. However, Table 12 indicates that the postvaccination titers were generally comparable across the two age strata, and that the resulting GMFR from baseline was 2.9 (95% CI = [2.1, 4.0]) among subjects 50 to 59 years of age and 2.0 (95% CI = [1.6, 2.6]) among subjects ≥60 years of age.

This preliminary summary from an ongoing clinical study corroborates the age-related immunogenicity results that were observed in the CMI Substudy of the Shingles Prevention Study. Furthermore, these data suggest that in subjects 50 to 59 years of age, the vaccine elicits a VZV-specific immune response that is at least as robust as that seen in older subjects.

Table 11

Summary of Baseline (Day 1) VZV Antibody Titers
by Age Stratum, Among All Subjects Included in the Preliminary Summary

| VZV Antibody Titer | Age 50 to 59 Years | | Age ≥60 Years | |
| | (N = 46) | | (N = 68) | |
	n	Titer (gpELISA units/mL)	n	Titer (gpELISA units/mL)
GMT (95% CI)	45	218.6 (160.1, 298.5)	68	385.7 (282.5, 526.7)
Median		230.3		287.5
Range		26.0 to 2166.2		35.4 to 28546.1
N = Number of subjects randomized. n = Number of subjects in each category.				

Table 12

Summary of VZV Antibody Titers by Age Stratum
(All Subjects with Serology Results)

Age Group	Endpoint	Time Point	Both Age Groups (N=114)		
			n	Observed Responses	95% CI
50 to 59	GMT	Day 1	45	218.6	(160.1, 298.5)
		Week 4	46	646.0	(448.3, 930.9)
	GMFR from Day 1	Week 4	45	2.9	(2.1, 4.0)
≥ 60	GMT	Day 1	68	385.7	(282.5, 526.7)
		Week 4	68	781.8	(583.9, 1046.8)
	GMFR from Day 1	Week 4	68	2.0	(1.6, 2.6)
N = Number of subjects vaccinated.					
n = Number of subjects contributing to the immunogenicity analysis.					

VZV-Specific Interferon-γ ELISPOT Assay

The VZV IFN-γ ELISPOT assay was performed in the Shingles Prevention Study and Protocols 007, 005, and 002 (Postdose 2 only). Due to the large number of invalid samples in Protocol 002, meaningful interpretation of results is not possible from that study. For the CMI Substudy population of the Shingles Prevention Study, the 6-week postvaccination response in the ZOSTAVAX™ group was significantly higher than in the placebo group, in terms of the GMC (69.8 SFC/10^6 PBMC in the ZOSTAVAX™ group, 31.8 SFC/10^6 PBMC in the placebo group) and the GMFR from Day 0 (2.1 in the ZOSTAVAX™ group, 0.9 in the placebo group) (Table 13). The estimated fold differences for both GMC and GMFR between the ZOSTAVAX™ group and the placebo group were 2.2 (95% CI = [1.9, 2.5]).

Table 13

Statistical Analysis of VZV IFN-γ ELISPOT Counts at 6 Weeks Postvaccination in the
CMI Substudy Participants
(The Shingles Prevention Study)

Endpoint	ZOSTAVAX™ (N=691)		Placebo (N=704)		Fold Difference[†] [ZOSTAVAX™/Placebo]
	n	Estimated Response[†]	n	Estimated Response[†]	(95% CI)
GMC	582	69.8	611	31.8	2.2 (1.9,2.5)
Geometric Mean Fold Rises from Day 0	582	2.1	611	0.9	2.2 (1.9,2.5)

[†] Calculated based on an ANCOVA model, which included the natural-log-transformed ELISPOT count or fold rise at 6 weeks postvaccination as the response variable, and treatment group, study site, treatment-by-study-site interaction, gender, age and natural-log-transformed ELISPOT count at Day 0 as independent variables. The fold differences for both GMC and Geometric Mean Fold Rise from Day 0 were the same in this setting.

The p-value for the treatment-by-study-site interaction was 0.3454. The p-value for vaccine effect was <0.001.

In Protocol 007, the estimated VZV IFN-γ ELISPOT GMC ratios of the ZOSTAVAX™ group to the placebo group were 1.8 (95% CI = [1.2, 2.6]) at 6 weeks Postdose 1 and 2.0 (95% CI = [1.2, 3.5]) at 6 weeks Postdose 2. The second dose of ZOSTAVAX™, which was administered 6 weeks Postdose 1, elicited a level of response in VZV IFN-γ ELISPOT comparable to that of the first dose. The secondary time points, including in the kinetics subset, suggested that the peak of the response occurred at 1 to 2 weeks postvaccination.

Protocol 005 enrolled subjects who had received VZV-containing vaccines several years prior to study entry. The GMCs were 75.1 SFC/10^6 PBMCs at Day 0 and 126.2 SFC/10^6 PBMCs at 6 weeks postvaccination, with a GMFR of 1.7 (95% CI = [1.5, 1.9]).

Based on the results across these studies, ZOSTAVAX™ elicited an immune response as measured by the VZV IFN-γ ELISPOT assay.

Exploratory Assays

Protocol 001 also evaluated CMI by assessment of IFN- γ, interleukin-2 (IL-2) and IL-10 cytokine responses by enzyme-linked immunosorbent assay (ELISA). These ELISA studies are considered exploratory in nature. Little dose response in IL-2 response was seen, but for IL-10, there appeared to be a slight dose response. Also in Protocol 001, IFN-γ ELISA results suggested that CMI responses were elicited at vaccine potencies beginning at ~19,000 PFU; this result provided part of the rationale for evaluating efficacy in the Shingles Prevention Study at an approximate expiry potency of ~20,000 PFU per dose.

3.2.2   Immune Response Following Two Doses of ZOSTAVAX™

Four-hundred seventy (470) subjects in Protocols 002, 005, and 007 received 2 doses of ZOSTAVAX™. The interval between doses varied in each protocol (42 days in Protocol 007, ~18 months in Protocol 002, and several years in Protocol 005). Protocol 002 utilized the VZV IFN-γ ELISPOT assay, but the results could not be interpreted meaningfully due to a large proportion of samples being invalid.

In Protocol 005, the VZV IFN-γ ELISPOT assay was used, and found to elicit a Postdose 2 immune response in these subjects. The GMC increased from a prebooster vaccination level of 75.1 SFC/10^6 PBMC to a postbooster vaccination level of 126.2 SFC/10^6 PBMC, which represented a GMFR of 1.7 (95% CI = [1.5, 1.9]).

In Protocol 007, both VZV IFN-γ ELISPOT responses and VZV antibody titers by gpELISA were measured, with the primary evaluation occurring at 6 weeks after each of the 2 doses. Overall, this study demonstrated that compared with placebo, 1 and 2 doses of ZOSTAVAX™ were immunogenic. In the VZV IFN-γ ELISPOT assay, the GMCs following Dose 1 (30.9 SFC/10^6 PBMC) and Dose 2 (37.1 SFC/10^6 PBMC) were similar; these responses were 1.8-fold (95% CI = [1.2, 2.6]; p-value=0.006) and 2.0-fold (95% CI = 1.2, 3.5]; p-value=0.012) higher than in placebo recipients at the respective time points. Furthermore, the VZV antibody GMTs following Dose 1 (561.9 gpELISA units/mL) and Dose 2 (559.2 gpELISA units/mL) were also similar; these responses were 1.7-fold (95% CI = [1.5, 1.9]; p-value<0.001) and 1.7-fold (95% CI = 1.5, 2.0]; p-value<0.001) higher than in placebo recipients at the respective time points.

Based on the results of Protocol 005 and Protocol 007, a dose of ZOSTAVAX™ either 42 days or several years following initial VZV vaccination elicits a VZV-specific immune response of a magnitude that is generally similar to that seen after an initial vaccination dose. These results support the potential benefit of a "booster" dose if one is determined to be required based on ongoing long-term efficacy follow-up.

3.2.3   Correlation of Immune Responses With Clinical Efficacy

In the Shingles Prevention Study, a subset of 1395 subjects were enrolled in the CMI Substudy. 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. Table 14 shows that for each vaccination group, the subjects who developed HZ had, on average, lower antibody titers than those who did not develop HZ. Following vaccination, subjects in the vaccine group who developed HZ had, on average, lower fold rises than did those who did not develop HZ. A Cox regression analysis showed a statistically significant inverse trend for risk of developing HZ with increasing antibody responses at 6 weeks postvaccination (p<0.001). Based on this model, a 1-log unit increase in antibody titers is associated with 38.0% (95% CI = [20.9, 51.5%]) reduction in the risk of HZ.

Table 14

Summary of gpELISA Titers at 6 Weeks Postvaccination Among the CMI Substudy
Participants by HZ Incidence Status for the San Diego and Denver Study Sites Combined

Endpoint	Subject Cohort (HZ Status After 6-Week Blood Sampling Date)	Zoster Vaccine (N=691)			Placebo (N=704)		
		n	Observed Response	95% CI	n	Observed Response	95% CI
GMT	Developed HZ	9	271.9	(161.9, 456.7)	23	181.6	(133.5, 246.9)
	Did not develop HZ	658	478.4	(444.6, 514.7)	661	296.2	(273.3, 321.1)
Geometric Mean Fold Rises from Day 0	Developed HZ	9	1.1	(0.9, 1.4)	23	0.9	(0.8, 1.1)
	Did not develop HZ	646	1.7	(1.6, 1.8)	650	1.0	(1.0, 1.0)

Note: subjects who developed herpes zoster prior to the 6-week bleed date are excluded from this analysis.
N = Number of subjects vaccinated in the CMI substudy.
n = Number of subjects contributing to the immunogenicity analysis.

Similarly, Table 15 shows that for each vaccination group, the subjects who developed HZ had, on average, lower VZV IFN-γ ELISPOT counts than those who did not develop HZ. A similar Cox regression analysis also shows a statistically significant inverse trend in the risk of developing HZ with increasing ELISPOT responses at 6 weeks postvaccination (p=0.017), although the trend was not as strong as that with antibody responses by gpELISA. Based on the model, a one-log unit increase in ELISPOT counts is associated with a 19.2% (95% CI = [4.6, 31.5%]) reduction in the risk of HZ.

Table 15

Summary of VZV IFN-γ ELISPOT Counts at 6 Weeks Postvaccination Among the CMI
Substudy Participants by HZ Incidence Status for the San Diego and Denver Study Sites
Combined

Endpoint	Subject Cohort (HZ Status After 6-Week Blood Sampling Date)	Zoster Vaccine (N=691)			Placebo (N=704)		
		n	Observed Response	95% CI	n	Observed Response	95% CI
GMC	Developed HZ	7	39.4	(7.9, 196.6)	21	17.4	(8.8, 34.4)
	Did not develop HZ	599	72.5	(63.9, 82.3)	621	32.2	(28.5, 36.4)
Geometric Mean Fold	Developed HZ	7	2.7	(0.6, 12.9)	21	1.1	(0.5, 2.2)
Rises from Day 0	Did not develop HZ	575	2.0	(1.8, 2.3)	590	0.9	(0.8, 1.1)

Note: subjects who developed herpes zoster prior to the 6-week bleed date are excluded from this analysis.
N = Number of subjects vaccinated in the CMI substudy.
n = Number of subjects contributing to the immunogenicity analysis.
The ELISPOT count is the number of spot-forming cells per 10^6 PBMC.

With respect to vaccine-induced immune responses, the Shingles Prevention Study demonstrated that 1) ZOSTAVAX™ significantly boosted VZV-specific immunity as measured by gpELISA and VZV IFN-γ ELISPOT assay; and 2) increases in these immune responses were associated with a lower risk of developing HZ. Compared with the VZV IFN-γ ELISPOT assay, the gpELISA was a better predictor of the vaccine effect and also has the operational advantages of superior reproducibility and reliability (less variability) throughout the range of values encountered.

3.2.4   Persistence of Immunity

Persistence of vaccine-induced VZV immunity was evaluated in the Shingles Prevention Study and Protocol 007. In the Shingles Prevention Study, samples were collected at 12, 24, and 36 months postvaccination.   The results of these analyses indicated that ZOSTAVAX™ recipients were able to maintain a higher fold-rise in VZV IFN-γ ELISPOT counts compared with placebo recipients up to 36 months postvaccination. The VZV antibody (gpELISA) titers were at their highest level at 6 weeks postvaccination, and then gradually decreased to a level slightly above, but still higher than, the prevaccination level.

In Protocol 007, samples were collected at 6 months Postdose 2 and analyzed in the VZV IFN-γ ELISPOT assay. The GMC in the ZOSTAVAX™ group at 6 months Postdose 2 was higher than both the baseline GMC and the GMC of the placebo group at 6 months Postdose 2, indicating persistence of the VZV-specific response in the ZOSTAVAX™ recipients.

4.   Clinical Safety

This section summarizes the safety data for ZOSTAVAX™ from 8 clinical studies (the Shingles Prevention Study [Protocol 004] and Protocols 001, 002, 003, 005, 007, 009, and VARIVAX™ Protocol 049). Following this overview, Section 4.1 provides a summary of the study population and extent of exposure to the vaccine. The analysis of adverse experiences, Section 4.2, includes the following summaries: adverse experiences in VZV-experienced subjects, with a focus on the Shingles Prevention Study (Section 4.2.1); adverse experiences in VZV-naïve subjects (Section 4.2.2); adverse experiences after ZOSTAVAX™ as a second dose (Section 4.2.3); and deaths, serious adverse experiences, and discontinuations (Section 4.2.4). Relevant postmarketing experience with VARIVAX™ in older adults is presented in Section 4.3. A discussion of the safety data (Section 4.4) completes this portion of the document.

More than 20,000 subjects receiving at least one dose of the final ZOSTAVAX™ formulation.   Most of the safety experience with ZOSTAVAX™ was single-dose administration to VZV-experienced subjects; however, several hundred subjects received a second dose of the vaccine. Also, a small number of VZV-naïve subjects were studied. In these subjects, the interest is in adverse experiences that reflect the replication of the attenuated vaccine virus, such as varicella-like rashes or fever.   All of these subjects were followed for safety, including all serious adverse experiences, for 42 days postvaccination, and for all vaccine-related serious adverse experiences throughout each study.   Approximately 5000 subjects (all subjects except those in the Routine Safety Monitoring Cohort of the Shingles Prevention Study) actively recorded all injection-site and systemic clinical adverse experiences through Day 42 postvaccination on a standardized Vaccination Repot Card (VRC). Oral temperatures were also recorded on the VRC, through either Day 21 or Day 42 postvaccination. The VRC used in the Shingles Prevention Study and Protocols 005, 007, 009, and VARIVAX™ Protocol 049 prompted for select adverse experiences, including certain injection-site adverse experiences (pain/tenderness, swelling, and, redness).   No systemic clinical adverse experiences were prompted for on the VRCs used in any of the protocols.

In addition to the large prelicensure safety experience with ZOSTAVAX™, safety data are available from the postmarketing experience for VARIVAX™.   The intended population for VARIVAX™ is VZV-naïve individuals.   The data for VARIVAX™ represent more than 10 years of postmarketing surveillance, with distribution of over 56 million doses worldwide.

The largest safety database for ZOSTAVAX™ is from the Shingles Prevention Study, in which 38,546 subjects were enrolled (19,270 received vaccine and 19,276 received placebo). All subjects in the Shingles Prevention Study were instructed to report adverse experiences that occurred during the first 42 days postvaccination; data on all deaths and all vaccine-related serious adverse experiences beyond 42 days postvaccination were also

collected. At the time of vaccination, 6616 subjects were enrolled into the Adverse Event Monitoring Substudy, in order to estimate the frequency of adverse experiences within 42 days postvaccination and the frequency of hospitalizations that occurred throughout the study. All 22 study sites participated in the Adverse Event Monitoring Substudy. All subjects enrolled in the Adverse Event Monitoring Substudy were given a standardized VRC, in order to facilitate recording of the adverse experiences occurring through Day 42 postvaccination. The other subjects enrolled in the Shingles Prevention Study, referred to as the Routine Safety Monitoring Cohort, were not required to complete a VRC, but were contacted by study site personnel on or around Day 43 postvaccination, to obtain information about rashes, other adverse experiences, and any symptoms of HZ.

The overall safety results demonstrate that ZOSTAVAX™ was generally well tolerated, with no adverse experiences, other than injection-site reactions, that occurred at a substantially higher frequency than following a dose of placebo.

4.1   Study Population and Extent of Exposure

Overall, 40,335 subjects ≥50 years of age were enrolled and received either active vaccine or placebo in the clinical studies that support the safety of the ZOSTAVAX™. The Shingles Prevention Study and Protocols 001, 002, 005, and 007 enrolled subjects who were ≥60 years of age. Protocol 009 enrolled subjects who were ≥50 years of age. Protocol 003 enrolled subjects in tropical countries who were ≥30 years of age, in an attempt to maximize recruitment of VZV-seronegative subjects. 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 number being ≥30 years of age.

Given the small numbers but relevant safety contribution, data were reviewed for VZV-seronegative subjects as young as 30 years of age. For the VZV-experienced population, data were reviewed for subjects ≥50 years of age. In total, 20,841 subjects ≥30 years of age were vaccinated with at least one dose of ZOSTAVAX™. Among these subjects, 20,697 were ≥50 years of age, of whom 20,456 received the final vaccine formulation intended for marketing. Additionally, 598 subjects received a second dose of ZOSTAVAX™ or high-titered VARIVAX™ (potency ~50,000 PFU/dose). Of the subjects receiving a second dose, 481 were ≥50 years of age. The study completion rate was 93.3 to 100% in the ZOSTAVAX™ protocols (Shingles Prevention Study and Protocols 001, 002, 003, 005, 007, and 009). Specific details of the subject accounting across studies can be found in Table 16. The study population was quite heterogeneous. More men than women were enrolled in the clinical studies; the mean age was close to 69 years in both genders. As noted in Section III.2.1, most subjects had one or more underlying medical conditions. Exclusion criteria focused generally on individuals known to be immunosuppressed. The study population was predominately White. Overall, ZOSTAVAX™ and placebo recipients were generally balanced with respect to age, race, and gender in these studies.

Table 16

Subject Accounting for Subjects ≥50 Years of Age
(Shingles Prevention Study and Protocols 001, 002, 003, 005, 007, and 009, and
VARIVAX™ Protocol 049)

	ZOSTAVAX™ (N=20,863[†])		Placebo (N=19,472)	
	n (%)		n (%)	
Gender				
Male	12,051	(57.8)	11,426	(58.7)
Female	8812	(42.2)	8046	(41.3)
Age (Years)				
Mean	69.3		69.4	
SD	6.5		6.3	
Median	69		69	
Range	50 to 99		59 to 94	
Race				
Asian	126	(0.6)	118	(0.6)
Black	412	(2.0)	420	(2.2)
Hispanic	298	(1.4)	251	(1.3)
Native American	37	(0.2)	32	(0.2)
Other	73	(0.4)	74	(0.4)
Unknown	3	(0.0)	4	(0.0)
White	19,914	(95.5)	18,573	(95.4)
[†]Includes 196 subjects from Protocol 005 who received a booster dose. Excludes 30 subjects from Protocol 002 that received Placebo at Dose 1 and ZOSTAVAX™ at Dose 2.				

The safety of ZOSTAVAX™ was evaluated at potencies as high as 203,000 PFU per dose. Except for a moderate increase in injection-site adverse experiences, the safety profile of the highest potency lot of vaccine was generally similar to that of the vaccine at lower potency.

4.2   Analysis of Adverse Experiences

4.2.1   Adverse Experiences in VZV-Experienced Subjects

Shingles Prevention Study

The primary source of safety data in the ZOSTAVAX™ development program is the Shingles Prevention Study. The data from this large-scale study demonstrate that among all subjects, the vaccine was generally well tolerated.

A summary of the adverse experiences reported for Day 0 through Day 42 postvaccination by the 6616 subjects (ZOSTAVAX™--3345 subjects; placebo--3271 subjects) in the Adverse Event Monitoring Substudy of the Shingles Prevention Study

indicates that one or more adverse experiences were reported by 58.0% of the subjects in the ZOSTAVAX™ group and 34.4% of the subjects in the placebo group (Table 17). The difference was driven mostly by injection-site reactions; the percentage of subjects reporting injection-site adverse experiences was greater in the ZOSTAVAX™ group (48.2%) than in the placebo group (16.6%). A statistical analysis found an increased risk of the following specific injection-site adverse experiences in the ZOSTAVAX™ group compared with the placebo group: erythema (35.7% versus 7.0%, p-value<0.001), pain/tenderness (34.5% versus 8.6%, p-value<0.001), and swelling (26.2% versus 4.5%, p-value<0.001). In addition, subjects in the ZOSTAVAX™ group had a higher frequency of pruritus and warmth at the injection site than did those in the placebo group. Most of the injection-site adverse experiences were reported as mild (~85%) and of brief duration, having resolved by Day 4 postvaccination.

The proportions of subjects with one or more systemic clinical adverse experiences in the 2 vaccination groups were similar (nearly 25% in each group). No statistically significant differences between ZOSTAVAX™ and placebo were seen in the risk for any systemic clinical adverse experiences occurring with an incidence ≥1%. In fact, the only systemic clinical adverse experiences reported with an incidence ≥2% in one or more vaccination groups were headache, respiratory infection, and rash.

A higher percentage of subjects in the ZOSTAVAX™ group reported vaccine-related systemic clinical adverse experiences than in the placebo group. However, the proportions were low in both groups (6.3% in the ZOSTAVAX™ group; 4.9% in the placebo group) and were not clustered in any body system or clinical syndrome. Among vaccine-related systemic clinical adverse experiences, headache (incidence, 1.4% in the ZOSTAVAX™ group and 0.9% in the placebo group) was the only event for which the lower bound of the 95% CI on the risk difference (ZOSTAVAX™ minus placebo) was greater than zero. In general, the systemic clinical adverse experience profiles were comparable between the ZOSTAVAX™ and placebo groups.

The summary of the incidence of elevated oral temperature (≥101.0°F [≥38.3°C]) occurring from Day 0 to 21 postvaccination in the Adverse Event Monitoring Substudy indicates that the percentages of subjects with elevated temperatures were low (<1%) and similar in the 2 vaccination groups (Table 18).

Table 17

Summary of Clinical Adverse Experiences in the Adverse Event Monitoring Substudy of
the Shingles Prevention Study
(Days 0 to 42 Postvaccination)

	ZOSTAVAX™ (N=3345)		Placebo (N=3271)	
	n	(%)	n	(%)
Number of subjects	3345		3271	
Subjects with safety follow-up	3326		3249	
Subjects without safety follow-up[†]	19		22	
Number (%) of subjects				
with no adverse experience	1397	(42.00)	2132	(65.62)
with one or more adverse experiences	1929	(58.00)	1117	(34.38)
injection-site adverse experiences	1604	(48.23)	539	(16.59)
systemic adverse experiences	820	(24.65)	768	(23.64)
with vaccine-related[‡] adverse experiences	1666	(50.09)	640	(19.70)
injection-site adverse experiences[§]	1602	(48.17)	536	(16.50)
systemic adverse experiences	209	(6.28)	160	(4.92)
with serious adverse experiences	64	(1.92)	41	(1.26)
with serious vaccine-related[‡] adverse experiences	0	(0.00)	1	(0.03)
who died	3	(0.09)	2	(0.06)
discontinued due to an adverse experience	0	(0.00)	0	(0.00)
discontinued due to a vaccine-related[‡] adverse experience	0	(0.00)	0	(0.00)
discontinued due to a serious adverse experience	0	(0.00)	0	(0.00)
discontinued due to a serious vaccine-related[‡] adverse experience	0	(0.00)	0	(0.00)

[†] Subjects who did not return their VRC or have any safety follow-up contact during the Days 0 to 42 postvaccination.
[‡] Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
[§] As determined by investigator assessment. For this Application, all injection-site adverse experiences were considered vaccine-related, regardless of investigator assessment.

Table 18

Number (%) of Subjects With Elevated Temperatures in the Adverse Event Monitoring
Substudy of the Shingles Prevention Study
(Days 0 to 21 Postvaccination)

	ZOSTAVAX™ (N=3345)		Placebo (N=3271)	
	n	(%)	n	(%)
Subjects with temperature follow-up	3229		3169	
Subjects with no temperature follow-up[†]	116		102	
Maximum temperature (oral)				
<101.0°F (<38.3°C) or normal	3147	(97.5)	3096	(97.7)
≥101.0°F (≥38.3°C) or abnormal	82	(2.5)	73	(2.3)
≥101.0°F (≥38.3°C)	12	(0.4)	19	(0.6)
Abnormal[‡]	70	(2.2)	54	(1.7)

[†] Subjects who did not return their VRC, or did not record temperatures on their VRC, or have any safety follow-up contact during the period from Days 0 to 42 postvaccination.
[‡] Included only those subjects who reported temperature as 'abnormal' and the maximum numeral temperature was <101°F (<38.3°C), if provided.
A subject who had at least one recorded temperature is considered to have follow-up of temperature.

Protocol 009 (ZOSTAVAX™ at High Potency)

Protocol 009 was designed to evaluate the safety profile of a high-potency lot of ZOSTAVAX™. The high-potency lot included in the study was specifically formulated to test ZOSTAVAX™ at the upper end of potency intended for clinical use. The study assessed the safety performance of the high-potency lot (203,244 PFU/dose) and a lower-potency lot (56,845 PFU/dose). Randomization was stratified by age group (50 to 59 years, n=185; ≥60 years of age, n=510). The primary safety endpoints for the study were: noninferiority of the high-potency lot compared with the lower-potency lot with respect to the incidence of vaccine-related serious adverse experiences during the first 42 days postvaccination; and the incidence in the high-potency lot of a composite endpoint of moderate or severe injection-site pain/tenderness/soreness or swelling occurring through Day 5 postvaccination, relative to a historical benchmark derived from the PNEUMOVAX™ 23[2] clinical development program.

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[2] PNEUMOVAX is a trademark of Merck and Co., Inc., Whitehouse Station, New Jersey, U.S.A.

With respect to the primary safety endpoints in Protocol 009, no vaccine-related serious adverse experience was reported in either vaccination group. For the primary endpoint on local tolerability, the incidence of moderate or severe injection-site pain or swelling occurring within 5 days postvaccination, the estimated incidence rate of the composite endpoint was higher in the higher-potency group than in the lower-potency group. However, the upper bound of the 95% CI in the higher-potency group was below the clinically meaningful limit that was pre-established based on the historical experience with PNEUMOVAX™ 23. Therefore, based on the prespecified criteria, the higher potency vaccine was considered well tolerated. The two potency groups were comparable with regard to all injection-site adverse experiences other than pain and swelling.

For the secondary safety endpoints, varicella or varicella-like rash with >100 lesions and HZ or HZ-like rash occurring within 42 days postvaccination, no statistically significant differences were observed between the 2 potency groups. Elevated temperatures (maximum oral temperature ≥ 101.0 °F) occurring within 21 days postvaccination were reported by <1% of the subjects in either group. The reported rates of systemic clinical adverse experiences and vaccine-related systemic clinical adverse experiences were comparable across the vaccination groups.

Among subjects 50 to 59 years of age, only injection-site adverse experiences were reported more frequently by subjects in the higher-potency group (82.9%) than in the lower-potency group (69.4%). The reported rates of systemic clinical adverse experiences (higher-potency group 40.7%; lower-potency group 45.2%) and of vaccine-related systemic clinical adverse experiences (higher-potency group 13.8%; lower-potency group 21.0%) were comparable across the vaccination groups. Among subjects ≥ 60 years of age, the percentages reporting adverse experiences in all 3 of these categories were comparable between the higher-potency and lower-potency groups (injection-site adverse experiences, 55.7% and 56.4%, respectively; systemic clinical adverse experiences, 36.3% and 37.2%, respectively; vaccine-related systemic clinical adverse experiences, 9.8% and 10.5%, respectively). For both vaccination groups, the incidence rates of these adverse experiences were generally somewhat lower in subjects ≥ 60 years of age than in subjects 50 to 59 years of age.

Overall, the higher potency of ZOSTAVAX™ appeared to be generally well tolerated in subjects 50 years of age and older. Although the higher-potency group had a somewhat increased rate of moderate or severe (almost all reports were moderate) injection-site pain or swelling compared with the lower-potency group, the observed rate was not considered clinically significant, based on the historical experience with PNEUMOVAX™ 23. Also, except for the frequency of transient injection-site adverse experiences of mild or moderate intensity, the vaccine was as well tolerated in subjects 50 to 59 years of age as it was in older subjects. Importantly, this study supports the acceptable safety and tolerability profile of ZOSTAVAX™ for potencies at the high end of the anticipated spectrum of clinical use.

<u>Findings Across Studies, Including VZV-like Rashes</u>

Across all studies included in this Application, except as noted above for Protocol 009, the proportions of vaccine recipients reporting injection-site and systemic clinical adverse experiences and elevated temperatures were generally similar to those reported by vaccine recipients in the Shingles Prevention Study.

The reported rates of VZV-like rashes within 42 days postvaccination were low in all of the clinical studies. In such situations, attempts were to be made to collect lesion specimens for analysis by PCR. A total of 99 varicella-like or HZ-like rashes were reported (82 from the Shingles Prevention Study and 17 from Protocols, 001, 002, 007, 009, and VARIVAX™ 049). In the Shingles Prevention Study, all varicella-like and HZ-like rashes that were VZV-positive by PCR analysis were found to be due to wild-type VZV. From Protocols 001, 002, 007, 009, and VARIVAX™ Protocol 049, 1 sample was confirmed to be wild-type VZV and 2 samples were positive for Oka/Merck strain. Details of the 2 rash cases from which lesion specimens revealed the Oka/Merck strain on PCR analysis are as follows: (1) a vaccine recipient from Protocol 001 reported a noninjection-site varicella-like rash with 21 lesions on Day 17, which lasted for 8 days. (2) a VZV-seropositive subject from VARIVAX™ Protocol 049 reported a noninjection-site varicella-like rash with 5 lesions on Day 8 Postdose 1, which lasted for 16 days.

4.2.2   Adverse Experiences in VZV-Naïve Subjects

Despite concerted effort in Protocol 003 (1148 potential subjects screened), the number of subjects in the ZOSTAVAX™ clinical studies who were VZV-seronegative and ≥ 50 years of age is quite limited. Therefore, all VZV-seronegative and VZV low-seropositive subjects from Protocol 003 (10 subjects) and all VZV-seronegative subjects ≥ 30 years of age (17 subjects) from VARIVAX™ Protocol 049 were combined for evaluation of safety. The reported rates of injection-site adverse experiences, systemic clinical adverse experiences, and elevated temperatures in these subjects were generally similar to the rates reported by the VZV-experienced subjects. Among the 27 subjects included in this population, 10 reported injection-site adverse experiences, 17 reported systemic clinical adverse experiences, and 2 reported an elevated temperature [≥ 101.0°F (≥ 38.3°C), oral]. The available data suggest that VZV-seronegativity is quite uncommon with increasing age. Based on a small number of subjects, no safety concern was evident.

4.2.3   Adverse Experiences After a Second Dose of ZOSTAVAX™

A total of 481 older adults received a second dose of ZOSTAVAX™ across 4 clinical studies (176 subjects in Protocol 002, 196 subjects in Protocol 005, 98 subjects in Protocol 007, and 647 subjects in VARIVAX™ Protocol 049, of whom 11 were ≥ 50 years of age). The rates of injection-site adverse experiences, systemic clinical adverse experiences, and elevated temperatures after a second vaccine dose were generally similar to those reported after a single dose. Five subjects (1.0%) who received 2 doses of ZOSTAVAX™ reported elevated temperatures Postdose 2. That the second dose is well tolerated could be

expected, given that the first dose is given to VZV-seropositive individuals and is also well tolerated. This second dose information will be relevant if durability studies point to the need for an additional dose. In addition, these data provide reassurance in the setting, not uncommon in the clinical care of older adults, of an unknown vaccination history.

4.2.4 Deaths, Serious Adverse Experiences, and Discontinuations

Serious Adverse Experiences and Deaths in the Shingles Prevention Study

For the total population enrolled in the Shingles Prevention Study, for whom all serious adverse experiences were reported through Day 42 postvaccination, no differences were seen in the number of subjects with serious adverse experiences (255 in the ZOSTAVAX™ group and 254 in the placebo group). In the Adverse Event Monitoring Substudy, a small increase in incidence of serious adverse experiences was observed among vaccine recipients (64 subjects), compared with placebo recipients (41 subjects), This was offset by the pattern observed in the Routine Safety Monitoring Cohort (191 subjects in the ZOSTAVAX™ group, 213 subjects in the placebo group). Of all serious adverse experiences reported through Day 42 postvaccination, only 4 (2 in the ZOSTAVAX™ group [polymyalgia rheumatica; exacerbation of asthma] and 2 in the placebo group [anaphylactic reaction; polymyalgia rheumatica]) were determined to be possibly vaccine related by the study investigator. Also, one subject in the placebo group developed a possibly vaccine-related serious adverse experience (Goodpasture's syndrome) on Day 53 postvaccination.

For the total population in the Shingles Prevention Study, from Day 0 to 42 postvaccination, 30 deaths (14 ZOSTAVAX™ recipients and 16 placebo recipients) were reported. Throughout the study, 1588 deaths (793 ZOSTAVAX™ recipients and 795 placebo recipients) were reported. For the overall study population, the cause of death was not recorded. However, the mortality rate of 4.0% observed in the study appears to be lower than might be expected in this age segment. No deaths were thought to be related to either the vaccine or HZ.

Deaths and Serious Adverse Experiences Throughout the ZOSTAVAX™ Program

In the remainder of the ZOSTAVAX™ clinical development program, the only other death that was reported was in VARIVAX™ Protocol 049, due to a motor vehicle accident in a subject who received ZOSTAVAX™.

Across all studies in the ZOSTAVAX™ development program, a total of 549 subjects reported serious adverse experiences (2 subjects in Protocol 001; 15 subjects in Protocol 002; 1 subject in Protocol 003; 509 subjects in the Shingles Prevention Study; 4 subjects in Protocol 005; 5 subjects in Protocol 007; 5 subjects in Protocol 009, 8 subjects in VARIVAX™ Protocol 049). Of these, only 5 subjects (all in the Shingles Prevention Study) reported serious adverse experiences that were determined to be possibly related to ZOSTAVAX™ and 2 subjects (in VARIVAX™ Protocol 049) reported serious

adverse experiences that were determined to be probably related to ZOSTAVAX™. No evidence of clustering by body system or clinical syndrome was noted in this small number of events. Also, across all studies, a total of 60 subjects discontinued due to a clinical adverse experience (2 subjects in Protocol 002; 29 subjects in the Shingles Prevention Study; 5 subjects in Protocol 007; 24 subjects in VARIVAX™ Protocol 049). Only the 2 subject discontinuations in Protocol 002 were determined by the investigator to be due to serious adverse experiences (pancreatic cancer; congestive heart failure, intestinal vascular insufficiency, cerebrovascular accident, and cardiac arrest). No subjects discontinued due to a clinical adverse experience in Protocols 003, 005, and 009.

4.3   Postmarketing Experience

The Pharmacovigilance Plan included in the license application re-emphasizes that the safety profile of the vaccine is acceptable, with no safety signals having been identified in any of the clinical studies. A multifaceted approach is proposed, including

*   routine passive pharmacovigilance,

*   expansion to ZOSTAVAX™ of the existing VZV Identification Program (VZV IP); Merck & Co., Inc. established the VZV IP in the United States in 1995 and in Europe in 2003 as an addition to routine passive surveillance. Through this program, clinical specimens, such as vesicle fluid or cerebrospinal fluid, can be analyzed by PCR in order to determine whether an observed event was associated with wild-type VZV or with Oka/Merck vaccine virus.

*   a registry to monitor outcomes in women who may inadvertently be exposed to ZOSTAVAX™ during pregnancy.

ZOSTAVAX™ has not yet been licensed in any country, and therefore, no postmarketing data are available. However, extensive postmarketing experience is available for VARIVAX™, which has been in the marketplace since 1995. A summary of postmarketing experience through 31-Dec-2004 in persons ≥50 years of age (64 reports). Fourteen reports included a medication error/accidental exposure; 12 of these 14 reports contained no other adverse experience. Two of the 14 reports included an adverse experience: 1 hour of eye irritation in a healthcare worker after ocular exposure, and a mild postvaccination rash that required antibiotics for a possible secondary infection (this report is also counted as a postvaccination rash).

The remaining reports included:

*   varicella or postvaccination rash (15 reports)

*   HZ (12 reports, of which 6 were reported as occurring after secondary transmission)

*   lack of seroconversion (11 reports)

*   mild injection-site reactions (5 reports)

*   varicella occurring after secondary transmission (3 reports)

- intermittent malaise, aches, and oral lesions for 6 months postvaccination (1 report)

- facial palsy after a second vaccine dose (1 report)

- autoimmune response (1 report)

- unexpected therapeutic effect in a patient who allegedly had chickenpox for 10 years, was vaccinated, and subsequently felt much better (1 report)

- disseminated varicella following a liver transplant that required parenteral acyclovir (1 report)

Among the 15 reports of rash or varicella occurring after vaccination, 9 occurred after a first dose, 1 after a second dose, and dose was not specified in 5 cases. With respect to reports of rash or varicella after vaccination in persons of all ages, the U.S. VZV IP has revealed that rashes occurring within 14 days of vaccination are more likely to be associated with wild-type VZV, whereas rashes occurring between 14 and 42 days after vaccination are more likely to identify the presence of Oka/Merck strain VZV. The 6 reports of HZ (Oka/Merck strain of VZV was not identified in any of these cases) occurring after administration of VARIVAX™. The postmarketing database contained 9 reports of possible transmission of vaccine strain VZV involving subjects ≥50 years of age—3 considered by the reporter to be cases of varicella after transmission and 6 reported as cases of HZ after transmission. With respect to cases of potential transmission of Oka/Merck VZV in subjects of all ages, the VZV IP program found that cases of secondary transmission occurred rarely. The vaccine strain has only been identified when the patient was a VZV-susceptible host who had close contact with a vaccine recipient with a postvaccination rash.

In summary, the review of postmarketing data identified very few adverse event reports in temporal association with the administration of VARIVAX™ for persons ≥50 years of age. The worldwide marketing experience available for VARIVAX™ strongly supports the general safety and tolerability of ZOSTAVAX™ in individuals ≥50 years of age.

4.4 Discussion of ZOSTAVAX™ Safety

The extensive safety data presented support the use of ZOSTAVAX™ in older adults without a known immunodeficiency. The number of subjects evaluated for safety was adequate to assess common, as well as relatively uncommon, adverse experiences. With 20,456 subjects ≥50 years of age having received the ZOSTAVAX™ formulation intended for marketing, the safety database provides 97.5% power to detect an adverse experience occurring with a rate of 1.8 per 10,000 persons (1 in every 5549 persons) and also provides 80% power to detect an adverse experience occurring with a rate of 0.8 per 10,000 persons (1 in every 12,717 persons). A thorough review of the safety data from each of the studies supports the conclusion of a clinically acceptable safety profile.

Subjects ≥60 years of age were selected in the large efficacy study because PHN, one of the primary endpoints, occurs infrequently in younger adults but occurs in more than one-third of patients with HZ who are ≥60 years of age. Clinical safety experience is available for subjects ≥50 years of age in Protocol 009 and VARIVAX™ Protocol 049. In particular, enrollment in Protocol 009 was stratified by age (50 to 59 years [n=185], ≥60 years of age [n=510]). This study, which also provided safety data with high-potency ZOSTAVAX™, showed that ZOSTAVAX™ was generally well tolerated in subjects 50 to 59 years of age. With the exception of an increase in the incidence of mild and moderate injection-site adverse experiences, the safety profile was similar to that observed in the more than 20,000 subjects who were ≥60 years of age. In view of the medical need and potential benefits of providing ZOSTAVAX™ to the general population beginning at 50 years of age, the Sponsor has included subjects ≥50 years of age in all of the recent ZOSTAVAX™ clinical studies, to further broaden the clinical experience with ZOSTAVAX™ in this age group.

In the Shingles Prevention Study, a subset of 6616 (17.2%) of the 38,546 subjects were enrolled in the Adverse Event Monitoring Substudy. Although the substudy represented only a fraction of those enrolled in the main efficacy study, the remaining 31,930 subjects (including 15,925 ZOSTAVAX™ recipients) were followed for serious and nonserious adverse experiences, elevated temperatures, rashes, and hospitalizations occurring within 42 days postvaccination. The safety experience in the Shingles Prevention Study is described extensively in Section III.4.2. Taken together, data on these 2 study cohorts in the Shingles Prevention Study were adequate to rule out the presence of clinically important vaccine-related adverse experiences beyond the expected injection-site reactions. A statistically significant but numerically small difference (6.3% versus 4.9%) in the observed rate of reported vaccine-related systemic clinical adverse experiences was not clustered by organ system or clinical syndrome.

Across the clinical studies conducted in the development program, data are available for 7 subjects with a prior history of HZ (protocol violators). In this limited number of subjects with prior HZ, no particular safety concerns were noted with the administration of ZOSTAVAX™. Although it is unknown what fraction of individuals with a past history of HZ would benefit from ZOSTAVAX™, such information, plus the acceptable safety profile of a second dose of ZOSTAVAX™ in Protocols 002, 005, and 007, could lend support for use of ZOSTAVAX™ in the setting of an unknown HZ or zoster vaccination history.

Immunocompromised patients are at increased risk of developing both HZ and its complications. Immunocompromise exists as a continuum. Although the clinical program enrolled subjects with diseases such as diabetes mellitus, psoriasis, and congestive heart failure, safety of ZOSTAVAX™ in overtly immunocompromised

individuals has not been established. Data are available for 5 immunosuppressed subjects (protocol violators) who were inadvertently enrolled into clinical studies (3 subjects with cancer and 2 subjects with known or suspected immune dysfunction). No specific safety concerns were reported following vaccination among this small number of immunosuppressed subjects.

No specific interaction studies with other vaccines were included in the Application, although a concomitant use study with inactivated influenza vaccine began enrollment in Sep-2005. Across the clinical studies in this Application, 40 subjects received pneumococcal polysaccharide vaccine, diphtheria/tetanus toxoids, hepatitis vaccine, influenza vaccine, Lyme disease vaccine, or tetanus toxoid within 42 days after receipt of ZOSTAVAX™. No adverse experiences of clinical significance were noted for these subjects.

5.   Summary of Benefits and Risks

The data presented confirm that ZOSTAVAX™ is immunogenic and has an excellent safety profile. The results of the large scale, double-blind, randomized, placebo-controlled, multicenter efficacy study support the proposed indications for prevention of HZ, prevention of PHN, and reduction of the pain burden associated with HZ.

No clinically important safety risks have been identified with the use of ZOSTAVAX™. Data from the 20,841 subjects who received ZOSTAVAX™ in clinical studies confirm that the vaccine has a very good safety profile. Beyond injection-site reactions, which are to be expected in association with any vaccine, no adverse experiences appeared in ZOSTAVAX™ recipients at a frequency substantially higher than that among placebo recipients; a small relative increase in the frequency of headache was observed in some studies, but not others. Given the established safety profile of VARIVAX™, largely in VZV-seronegative populations, the favorable safety experience with ZOSTAVAX™ among VZV-seropositive hosts is not surprising. VZV-like rashes, which could reflect a potential safety concern for vaccine recipients or susceptible, high-risk individuals with whom they come in contact, have been uncommon in ZOSTAVAX™ clinical studies. These rashes have been reported at a rate several-fold lower than has been seen in conjunction with VARIVAX™. Investigators were requested to obtain swab specimens from subjects who developed VZV-like rashes after vaccination. The available PCR results, for 54 of the 82 VZV-like rashes reported, showed that nearly all VZV-positive specimens were wild-type virus; only twice, among over 20,000 ZOSTAVAX™ recipients, was the Oka/Merck strain identified in the PCR analysis. Thus, the overall safety profile of ZOSTAVAX™ in clinical studies provides no indication of the potential for a significant risk, were widespread vaccination to commence.

Despite the availability of numerous therapeutic modalities, prevention and optimal treatment for HZ and PHN present a significant unmet medical need. No satisfactory preventive options are currently available. Early initiation of treatment with an antiviral agent such as acyclovir, famciclovir, or valacyclovir has been shown to reduce the severity of acute HZ, as defined by the time to HZ rash healing, and the duration of HZ-associated pain. However, in order to gain maximal benefit from the currently licensed antiviral drugs, patients with possible HZ must be aware that they need to seek medical attention early in the course of the illness. Furthermore, no controlled, double-blind studies of antiviral agents have been performed to show an impact on the incidence of PHN per se, and so the effect on PHN is uncertain, although prompt initiation of antiviral therapy can shorten the duration of PHN [63; 68; 69; 70; 71; 72; 73; 74]. In well-designed studies, corticosteroids demonstrated a modest effect on the acute phase of HZ, but no reduction in the frequency or severity of PHN [4; 36; 69; 75]. Treatment of HZ that combines antiviral drugs and corticosteroids also does not prevent PHN. Prolonged neural blockade, with or without the addition of corticosteroids, has been shown to reduce duration of HZ pain in some studies. Although this procedure may offer a minor protective effect against PHN, the necessary duration of hospitalization and potential for adverse effects make such treatment inappropriate for most patients and healthcare systems [76; 77; 78].

PHN is a common cause of intractable, debilitating pain in the elderly which, once established, is notoriously difficult to treat. The current management of PHN includes a range of pharmacological, invasive, and other medical strategies that are frequently unsuccessful. Medications commonly used, such as tricyclic antidepressants (e.g., amitriptyline), agents with anticonvulsant properties (e.g., gabapentin), and strong opiates (e.g., morphine, oxycodone) are partly effective, but are typically associated with high rates of adverse events, especially in the elderly, that can further disrupt the day-to-day functioning of patients with PHN [45; 79; 80; 81]. Even recently licensed drugs, such as gabapentin and pregabalin, have shown only a modest reduction in pain among patients with PHN, and have marked side effects that limit their utility [36; 41; 44; 79; 81; 82]. Adjunctive topical use of lidocaine patches or capsaicin may be helpful to some patients. Intrathecal methylprednisolone has been shown to be effective in one study [83], but confirmatory evidence is lacking and such treatment is considered dangerous by some authorities [84; 85]. Because of the limited efficacy and tolerability of the available medications, PHN often results in fatigue, insomnia, depression, anxiety, emotional distress, and interference with social and functional daily activities [76; 86; 87; 88] and has been anecdotally reported to provoke suicidal intent in some patients. No currently available medical treatments or practicable interventions are known that can consistently prevent PHN.

In addition to being difficult medical conditions to manage effectively, HZ and PHN are more common than is widely appreciated. As noted in Section III.1, an estimated 1 million cases of HZ occur annually in the United States. The number of prevalent cases of PHN cannot be determined with any precision. However, based on published literature, some authors have estimated a prevalence of 500,000 to 1 million cases in the United States [24; 42; 89].

Every year, an estimated 50,000 to 60,000 hospitalizations are related to HZ (12,000 to 19,000 as the primary reason for hospitalization) in the United States [53]. The average length of stay for HZ-related hospitalizations is approximately 5 to 7 days in the United States [53], and tends to increase with advancing age [16; 23]. Given the often unsatisfactory results associated with treatment and the prospect of debilitating, chronic pain, the impact of ZOSTAVAX™ in the pivotal efficacy study, in which it lessened acute-and-chronic pain (the HZ pain BOI) by more than 60%, reduced the incidence of HZ by more than one-half, and reduced the incidence of PHN by two-thirds, is an impressive and important set of clinical findings.

Other factors in the execution of the efficacy study bear mention. For patients who present early in the course of HZ, antiviral therapy is the standard of care. The Shingles Prevention Study specified the provision of famciclovir routinely and allowed analgesic medications ad lib for subjects with suspected HZ. Of note, these highly motivated subjects who developed HZ in this study received frequent and comprehensive health assessments, while under the care of HZ experts, who would be expected to treat HZ pain maximally. Despite the presumed aggressive case management, the benefits of ZOSTAVAX™ were still very dramatic. In this respect, the Shingles Prevention Study gave a realistic, perhaps even conservative assessment, of the benefit of a vaccine as it would be experienced in routine clinical practice.

Although the clinical efficacy study included only subjects ≥60 years of age, the epidemiological data presented in Section III.1 and the information presented in Section III.3.1 provide strong support for adopting 50 years as the age at which routine ZOSTAVAX™ vaccination should begin. In immunocompetent young adults, the incidence of HZ is fairly low, and the disease typically mild. The sharp age-related increase in HZ incidence begins in the sixth decade of life (i.e., 50 to 59 years of age), with an approximate doubling of the incidence relative to that for persons 40 to 49 years of age [14; 16; 19]. Using HZ incidence rates from Hope-Simpson and population data for 2005, an estimated 200,000 cases of HZ occur every year in the United States in individuals 50 to 59 years of age, i.e., ~21% of all HZ cases. In comparison, ~40% of all HZ cases occur in individuals ≥60 years of age. Therefore, vaccination beginning at 50 years of age (rather than 60 years of age) could increase by approximately 50% the number of HZ cases that could be prevented or ameliorated. In the Shingles Prevention Study, VE_{HZ} was higher (64%) in subjects 60 to 69 years of age than in subjects ≥70 years of age (38%). Thus, the overall VE_{HZ} of 51% observed in the Shingles Prevention Study is likely to be a conservative estimate for the 50- to 59-year age category. In addition, the GMT of VZV antibodies by gpELISA at 6 weeks postvaccination was 498.7 gpELISA units/mL in subjects 60 to 69 years of age and 445.2 gpELISA units/mL in subjects ≥70 years of age. The corresponding fold-rise from Day 0 to 6 weeks postvaccination was 1.8 in subjects 60 to 69 years of age and 1.6 in subjects ≥70 years of age. Similar age-related findings were observed in other

ZOSTAVAX™ clinical studies. A lot of ZOSTAVAX™ that was used in the Shingles Prevention Study and also in ZOSTAVAX™ Protocol 002, was administered in individuals <60 years of age in VARIVAX™ Protocol 049. In subjects 50 to 59 years of age (n=10), the GMT at 6 weeks postvaccination was 578.5 gpELISA units/mL, with a GMFR of 2.8 from prevaccination to postvaccination. Also, a newly-available preliminary summary from an ongoing study, which showed a 2.9-fold GMFR in subjects 50 to 59 years of age and a GMFR of 2.0 in subjects ≥60 years of age. Although based on a small number of subjects 50 to 59 years of age, these immunogenicity results suggest that ZOSTAVAX™ would stimulate immune responses in persons 50 to 59 years of age that are at least as strong as the immune responses in vaccinees ≥60 years of age. Protocol 009, in which enrollment was stratified by age in a 1:2 ratio, resulted in a total enrollment of 185 subjects between 50 and 59 years of age. The study concluded that the vaccine was well tolerated in adults 50 years of age or older, although injection-site reactions of mild and moderate intensity were reported at a somewhat higher rate in subjects 50 to 59 years of age than in subjects ≥60 years of age. The potential safety risk in this age group is minimal, based on the available data.

In addition to the substantial medical impact, vaccinating younger adults could prevent work productivity loss, because the majority of individuals (~70% in the United States) 50 to 59 years of age are employed [90]. Assuming an average of 3 to 5 days of work lost per HZ case (likely to be a conservative estimate) [91], an estimated 400,000 to 700,000 work days are lost due to HZ every year among 50- to 59-year-olds alone in the United States.

To fully assess the vaccine benefit versus risk, it is important to examine patient groups who were not included in the clinical studies. Immunocompromised individuals were excluded from enrollment in all studies, and the presently available data cannot support ZOSTAVAX™ vaccination of any individuals with immunocompromising conditions.

Several questions remain unanswered about ZOSTAVAX™. Most importantly, the durability of vaccine efficacy is not known. In the Shingles Prevention Study, the efficacy remained relatively stable through Year 4 postvaccination, after an initial drop in the first ~1 year. However, the duration of the effect and the potential need for a "booster" dose remain an unknown. A long-term persistence study to follow subjects from the Shingles Prevention Study for 5 additional years is beginning in the fall of 2005.

The potential benefit of a "booster" dose of ZOSTAVAX™ can be inferred from the current database. Although not seeking an indication for revaccination, safety and immunogenicity data for several hundred subjects who received a second ZOSTAVAX™ vaccination have been provided. In these studies, no safety concerns arose subsequent to a second ZOSTAVAX™ dose, as would be expected given the safety profile of the first dose administered to individuals who are already VZV-seropositive. Furthermore, a second dose of ZOSTAVAX™ after a short interval (in Protocol 007) or a long interval (in Protocol 005) elicited immune responses generally similar to those seen after a first dose. Therefore, should a drop-off in vaccine efficacy over time be observed in long-term follow up studies, the available data suggest an immunologic benefit from a second dose.

The demonstration that a second dose of ZOSTAVAX™ is well tolerated has an additional, very practical benefit. Self-report of vaccination status by older adults is frequently unreliable. One study of self-reported pneumococcal vaccination status in adults ≥65 years of age found positive and negative predictive values of only 78% and 61%, respectively [92]

Interaction (concomitant use) studies with commonly administered adult vaccines were not included in the license application. However, a concomitant use study with influenza vaccine is being conducted in the fall of 2005.

In addition, it is unclear whether ZOSTAVAX™ should be administered to any persons with a past history of HZ. Although it is arguable that the vaccine would be unlikely to benefit those with a history of HZ in the recent past, older adults with a history of HZ many years in the past could be at nearly the same risk as people of the same age who never had an episode of HZ. Despite the limited benefit that might accrue, it appears that there is little cause for concern from a safety standpoint, should the vaccine be administered to a person with prior HZ, since even those without a prior history of HZ have substantial VZV-specific immunity at baseline.

Overall, ZOSTAVAX™ provided strong evidence of efficacy in a population that was representative of the population for which it is intended, without an offsetting safety risk. The vaccine has demonstrated a highly favorable benefit/risk ratio.

6.   Overall Conclusions

The efficacy data from the Phase III study support the following conclusions:

1. Compared with placebo, ZOSTAVAX™ significantly reduces the incidence of HZ.

2. Compared with placebo, ZOSTAVAX™ significantly reduces the incidence of PHN.

3. Compared with placebo, ZOSTAVAX™ significantly reduces the burden of illness related to HZ pain.

4. Compared with placebo, ZOSTAVAX™ significantly reduces the duration of clinically significant pain associated with HZ.

5. Compared with placebo, ZOSTAVAX™ significantly reduces the overall severity of ADLI; however ZOSTAVAX™ does not significantly reduce the risk of Substantial ADLI, based on a definition of a combined ADL score of >2 for >7 days, beyond the reduction in HZ incidence.

6. Compared with placebo, ZOSTAVAX™ efficacy against HZ and PHN persists through 4 years of follow-up.

The immunogenicity data from Phase II and Phase III studies support the following conclusions:

1. Among varicella-history positive, HZ history-negative adults ≥60 years of age given 1 dose of ZOSTAVAX™ or placebo, ZOSTAVAX™ elicits significantly higher VZV-specific immune responses at 6 weeks postvaccination compared with placebo as measured by gpELISA and VZV IFN-γ ELISPOT assay.   The 6-week postvaccination results and geometric mean fold rises from Day 0 to Week 6 were somewhat better in the 60-to-69 age group than in the ≥70 age group.

2. Immune responses, as measured by gpELISA and VZV IFN-γ ELISPOT, persist above baseline titers up to 36 months postvaccination.

3. The VZV antibody response measured by gpELISA (titer and fold rise from baseline at 6 weeks postvaccination) correlates reasonably well with protection against HZ. To a lesser extent VZV IFN-γ ELISPOT also correlates with protection against HZ.

The safety data from the Phase II and III clinical studies of ZOSTAVAX™ support the following conclusions:

1. ZOSTAVAX™ is generally well tolerated in adults ≥50 years of age.

2. Following a dose of ZOSTAVAX™, the incidence of injection-site reactions is consistently higher than the incidence following a dose of placebo, but these adverse experiences are generally mild in intensity and of short duration.

3. The overall incidence of systemic clinical adverse experiences following a dose of ZOSTAVAX™ is similar to that following a dose of placebo. The incidence of vaccine-related systemic clinical adverse experiences is slightly higher after a dose of ZOSTAVAX™ than after a dose of placebo, but no individual adverse experience is consistently reported at a higher rate among ZOSTAVAX™ recipients.

4. Following a dose of ZOSTAVAX™, both varicella-like rashes and zoster-like rashes are uncommon, and are observed at a frequency substantially lower than that seen in VZV-seronegative individuals after receipt of VARIVAX™.

7.   List of References

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