

National PBM Drug Monograph
Zoster Vaccine
Varicella Virus Vaccine Live (Oka/Merck)
(Zostavax[®])
November 2006

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

This monograph is a review of zoster vaccine live (Oka/Merck) (ZVx), which was approved by the Food and Drug Administration (FDA) on May 25th, 2006 for the prevention of herpes zoster (HZ) in individuals 60 years of age and older.

One major efficacy trial (Department of Veterans Affairs Cooperative Study #403: the Shingles Prevention Study, SPS [VA CSP #403], Merck Protocol 004) and one additional safety trial (Merck Protocol 009) were included in the FDA clinical briefing document for the proposed product.

Dosage and administration: A single 0.65-ml subcutaneous dose of ZVx (minimum potency, 19,400 plaque-forming units) should be given within 30 minutes of reconstitution. The need for booster doses has not yet been established.

Efficacy: The SPS, conducted by the VA Cooperative Studies Program in collaboration with the NIAID and Merck, enrolled 38,546 participants and showed that immunization of relatively healthy adults aged 60 years or older significantly decreased the burden of illness due to herpes zoster (HZ BOI; a composite measure of incidence, severity, and duration of HZ-associated pain) by 61.1%, the incidence of postherpetic neuralgia by 66.5% (from 1.38 to 0.46 cases per 1000 person-years), and the incidence of herpes zoster (HZ) by 51.3% (from 11.12 to 5.42 per thousand person-years) during the 3 years following vaccination, as compared with placebo. There was a trend toward decreasing efficacy in all three efficacy measures over time (during the first 3 years after vaccination). ZVx efficacy for HZ BOI and for the incidence of HZ were lower in participants ≥ 70 years of age than in those 60 to 69 years of age, but efficacy for PHN was comparable in the two age groups. This age-related decrease in ZVx efficacy was apparent in participants over 75 years of age and in those over age 80, but the limited number of participants in these age groups precluded a definitive assessment of efficacy.

Safety: In VA CSP#403, the Rates of SAE during the day 0 to day 42 safety assessment period were identical at 1.4% in the total population of vaccine and placebo recipients, with data from active surveillance obtained from more than 93% of the participants in each treatment group. In the AE Monitoring Substudy, in which a subset of the study participants were asked to complete a Vaccine Report Card recording all adverse events during the 42-day safety assessment period of VA CSP #403, the rates of SAEs reported to occur within 42 days postvaccination were significantly higher in ZVx recipients as compared with placebo recipients (1.9% and 1.3%, respectively, absolute difference, 0.7%, $p = 0.03$), particularly in older participants (≥ 70 years of age). There was no significant difference between treatment groups in SAEs and overall mortality in the overall study cohort, and only 2 SAEs were considered by investigators to be related to

study treatment. Currently, there is no evidence that the difference was due to ZVx. Similarly, in Merck Protocol 009, the results showed no specific pattern of SAEs, except more SAEs were observed in the high-dose group than in the low-dose group (4 versus 1 participant, respectively). The most common adverse events were injection site reactions, which were mostly mild and transient. There was no significant treatment difference in the rates of systemic vaccine-associated adverse events. **On December 15, 2005, the FDA clinical reviewer concluded that, because of deficiencies in the Automated Telephone Response System (ATRS) follow-up in VA CSP #403, it was difficult to make conclusions about the relative safety of ZVx (0.5 ml) from day 0 to 42 postvaccination (however, data on SAEs from day 0 through day 42 postvaccination were actively collected from more than 93% of the total study population, which includes participants enrolled in the Adverse Event Monitoring Substudy). For day 43 to end-of-study safety follow-up, the FDA clinical reviewer considered interpretation of the data to be limited since the safety data was passively collected and the nature of the safety data was inconsistent. The manufacturer (Merck & Co., Inc.) has committed to conduct a postmarketing placebo-controlled randomized trial to assess the rate of serious adverse experiences in vaccinees, stratified by age less than 80 years old and 80 years of age and older.**

Data Compilation: The number-needed-to-vaccinate for benefit suggests that 59 (95% CI: 37 to 143) individuals would need to be vaccinated to prevent HZ in one additional person over 3.1 years. Until additional information on the incidence, nature, and time course of the SAEs becomes available for a 3-year period, it is difficult to estimate the number-needed-to-vaccinate for major harm (NNVH).

Pharmacoeconomic Analysis: If the cost of ZVx is assumed to be \$111 per dose and the calculated number-needed-to-vaccinate to prevent one additional case of HZ is 59, then the vaccine acquisition cost associated with HZ prevention would be over \$390 to \$594 million over a 3-year period (FY06 to FY08) or \$6549 for each vaccinee who will benefit.

Conclusions: ZVx is the only agent shown to prevent HZ. ZVx was associated with moderate to large *relative* reductions in the incidence of HZ, while the numerical, absolute reduction was somewhat small but perhaps acceptable for preventive therapy. Furthermore, the 66.5 % reduction in the incidence of PHN in both age strata is clinically important, especially for the older veteran population. While no difference between vaccine and placebo recipients in the rate of SAE was observed in the entire study population, a significantly higher rate of serious adverse events was observed in ZVx versus placebo recipients in a 17% subset of the study participants enrolled in an AE Monitoring Substudy. This difference was attributed to chance; however, it is difficult to completely discount the possibility of a greater risk of major harm due to ZVx. There will likely be important pharmacoeconomic implications to consider before undertaking any zoster vaccination program in the VHA. On December 15, 2005, **the FDA Vaccines and Related Biological Products Advisory Committee** agreed that there was sufficient evidence of efficacy (incidence of HZ) only for the 60- to 80-year age group. With the qualification that the manufacturer provide additional information on SAEs, they agreed there was sufficient evidence of safety in the same age group. The evaluation of ZVx remains to be completed, specifically in regard to the higher risk of SAEs observed in the vaccine group and to cost-effectiveness analyses.

Introduction

More than 15 years after the concept of boosting cell-mediated immunity to varicella zoster virus was introduced,¹ a large landmark trial, the Shingles Prevention Study (SPS), was conducted by the VA Cooperative Studies Program to evaluate the efficacy and safety of varicella zoster virus vaccine live (Oka/Merck) in the prevention of herpes zoster (HZ) and postherpetic neuralgia (PHN). Although there is still a question of whether the incidence of HZ will increase or decrease following widespread varicella vaccination,²⁻⁴ there is probably little doubt that the availability of an effective zoster vaccine will be a major public health advancement. Since there is no other preventive therapy for HZ and the available antiviral agents and corticosteroids do not uniformly prevent PHN, a zoster vaccine would be a novel method of prophylaxis against HZ, particularly in older individuals (e.g., ≥ 60 years old) who are at higher risk than younger adults of both developing HZ and such debilitating complications as PHN, as well as experiencing more severe symptoms of HZ. Considering the important public health implications of a zoster vaccine in the U.S. veteran population, the Veterans Health Administration national Pharmacy Benefits Management Strategic Healthcare Group has performed this accelerated review of Merck's live attenuated zoster vaccine (ZVx).

The purposes of this monograph are to (1) evaluate the current evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating ZVx for possible addition to the VA National Formulary; (2) define its potential role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

ZVx was formulated using the same virus seeds, drug substance process, and varicella vaccine bulk as those used for the varicella component in Merck's FDA licensed vaccines, Varivax™ and ProQuad™. Whereas ZVx is intended for prevention of HZ in older adults, Varivax and ProQuad are indicated for vaccination against varicella in children 12 months of age or older and 12 months to 12 years of age, respectively (Table 1).

Table 1 Varicella Virus Vaccine Live (Oka/Merck) Products

Trade Name	Zostavax	Varivax	ProQuad
Common Name	Zoster vaccine	Varicella vaccine	Measles, Mumps, Rubella, and Varicella Vaccine, live, attenuated (MMRV)
Current FDA Status	Review in process	Approved	Approved
VVVL Dose (PFU)	19,400–207,000	1350–17,000	$\geq 3.99 \log_{10}$ /
Volume per Dose (ml)	0.65	0.5	0.5
Number of Doses	1	1–2 (age 12 mo–12 y) 2 (age ≥ 13 y)	1 (age 12 mo–12 y)
Indication	Prevention of herpes zoster (shingles) in individuals 60 years of age and older.	Vaccination against varicella in individuals 12 months of age and older	Simultaneous vaccination against measles, mumps, rubella, and varicella in children 12 months to 12 years of age

PFU, plaque-forming units; VVVL, Varicella virus vaccine live

In preliminary studies, higher potency vaccines were necessary to induce a significant cell-mediated immune response to VZV in older adults. The minimum potency of the proposed ZVx is at least 14 times greater than the minimum potency of the vaccine approved to prevent varicella or chickenpox (Varivax). There is no evidence that the lower-potency vaccines would be

Zoster vaccine NMEM (Final 111606)

Updated version may be found at www.pbm.va.gov or vawww.pbm.va.gov

efficacious in older adults in the prevention of herpes zoster or postherpetic neuralgia, and they are not recommended for this use.⁵

Since ZVx is a live vaccine, its potency will decay over time because of storage conditions. Potency will also vary between lots; however, the minimum dose indicated on the proposed labeling will be at least 19,400 plaque-forming units (PFU).

Indication(s) and Potential Off-label Uses

FDA-approved indication

Prevention of herpes zoster (shingles) in individuals 60 years of age and older.

Not indicated for the treatment of herpes zoster or postherpetic neuralgia.

Potential off-label uses of zoster vaccine for other than proposed indication

The SPS also demonstrated that ZVx reduced the incidence of PHN in participants ≥ 60 years of age, and that efficacy for PHN did not decrease in participants ≥ 70 years of age compared with those 60 to 69 years of age. .

Current VA National Formulary Alternatives

None. The authors of the SPS (VA CSP #403) recommended against using vaccines with lower potencies than that of the proposed zoster vaccine for prevention of HZ because of the lack of evidence to support their use.

Dosage and Administration

The FDA approved a higher dose (0.65 ml) of ZVx (minimum potency, $\geq 19,400$ PFU) than that used in the SPS (dose, 0.5 ml). Single doses should be given by subcutaneous injection.

ZVx, available as a lyophilized powder in single-dose vials, must be protected from light. It should be stored frozen at -15°C or colder but during shipping, it should be maintained at -20°C or colder. ZVx should be reconstituted immediately upon removal from the freezer and administered immediately after reconstitution to minimize loss of potency. Only the supplied preservative-free diluent (either refrigerated at $2-8^{\circ}\text{C}$ or at room temperature) should be used to reconstitute the vaccine.

Reconstituted vaccine should not be frozen and should be discarded after 30 minutes.

Efficacy

The preliminary evidence of the efficacy of ZVx was obtained through literature searches of PubMed (1966 to January 2006), the Cochrane Central Registry of Controlled Trials (to January 2006), FDA medical^{6,7} and statistical⁸ reviews, and transcripts of the December 15, 2005 FDA Vaccines and Related Biological Products Advisory Committee meeting.⁹

A total of 7 trials (Protocols 001 to 005, 007, and 009) were submitted to the FDA in support of the NDA-proposed indication of single-dose immunization of adults ≥ 50 years (note that the only efficacy data is in participants ≥ 60 years of age) for prevention of herpes zoster and postherpetic neuralgia, and reduction of acute or chronic zoster-associated pain.

The major efficacy trial (SPS, VA Cooperative Study #403: "The Shingles Prevention Study" / Merck Protocol 004) and one safety trial (Merck Protocol 009) were included in the FDA clinical briefing document of the proposed product.⁶ VA CSP #403 evaluated a 0.5-ml dose containing 22,000 to 62,500 PFU of ZVx in participants aged ≥ 60 years. The safety trial (Protocol 009) was designed to support an indication for use of a higher potency and dose (207,000 and 58,000 PFU per 0.65 ml) in relatively younger participants aged 50 to 59 years.

Efficacy Measures (Shingles Prevention Study, VA CSP #403 / Merck Protocol 004)

Primary efficacy measures

HZ Burden of Illness Score (BOI): a composite measure of incidence, severity, and duration of pain and discomfort, including allodynia and severe pruritus, caused by HZ, as measured on a Brief Pain Inventory (BPI) modified for HZ (Zoster BPI, ZBPI). The BOI score was calculated by adding the HZ Severity of Illness Scores of all participants within the treatment group (the HZ Severity of Illness Score is the area under the pain severity-by-duration curve for each participant who developed HZ; participants who did not develop HZ were assigned a score of “0”). Mean pain severity (0 to 10 scale, where 10 = Worst pain) was derived from the weekly worst pain score multiplied by 7 days. The HZ BOI was chosen as the study's primary endpoint because it represented the best measure of the total clinical burden of HZ in older persons afflicted with the disease, and because the VA CSP #403 Planning Committee, Merck and the FDA all agreed that a reduction in the HZ BOI would provide a clinically relevant measure of vaccine efficacy that would reflect any combination of a reduction in the incidence, severity, or duration of pain and discomfort caused by HZ. The VA CSP #403 Planning Committee and Merck developed and validated the ZBPI and the HZ BOI scoring method in preparation for the SPS and showed that HZ Severity of Illness Score correlates with decrements in quality of life and activities of daily living.¹⁰

Incidence of PHN: HZ-associated pain and discomfort rated ≥ 3 (0 to 10 scale) persisting or appearing at least 90 days after onset of HZ rash. The time criterion for defining PHN was revised during the trial from 30 days to 90 days (both cutoffs yielded similar results).

Secondary efficacy measures

Incidence of HZ: number of *evaluable* HZ cases per 1000 person-years of follow-up. Evaluable cases of HZ were confirmed using a hierarchical diagnostic approach, using PCR, VZV viral culture, and adjudication by a Clinical Evaluation Committee, which evaluated all suspected cases. *Suspected cases of HZ* were defined as a rash with unilateral dermatomal distribution and at least one of the following: vesicles in the area of the rash and/or pain in the area of the rash.

Duration of clinically significant HZ pain: number of days between the first day after rash onset when the participant had a “worst pain” score of ≥ 3 (as reported on either the Initial Zoster Impact Questionnaire [IZIQ] or the Zoster Brief Pain Inventory [ZBPI]) and the first visit when the “worst pain” score reported on ZBPI was < 3 and remained < 3 for the remainder of the follow-up period (≥ 182 days after HZ rash onset). The ZBPI “worst pain in the last 24 hours” had been previously validated and shown to correlate with changes in responses to health status questions.

Substantial Activities of Daily Living Interference (ADLI or SADLI): combined ADLI score ≥ 2 for ≥ 7 days, beyond reduction in HZ in the 6-month period following HZ rash onset. The ADLI scale consisted of 7 items, each scored on a 0 to 10 scale where 10 = maximum interference): general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life. Although this measure was listed in the FDA clinical review briefing document,⁶ no results were reported.

Severity of HZ. An HZ Severity of Illness Score was defined as the area under the ZBPI worst pain response-versus-time curve during the 182-day study period.

Summary of Efficacy Findings

The SPS enrolled 38,546 participants, of whom 20,747 were 60 to 69 years of age and 17,799 were aged 70 years and older. The Merck Protocol 004 clinical-statistical report indicated that immunization of relatively healthy adults aged 60 years or older (95% of whom were white) with

a single 0.5-ml subcutaneous dose of ZVx significantly decreased the BOI score by 61.1% during the 3 years following vaccination, the incidence of postherpetic neuralgia by 66.5% (from 1.38 to 0.46 cases per 1000 person-years), and the incidence of herpes zoster by 51.3% (from 11.12 to 5.42 per thousand person-years) as compared with placebo (Table 2).

Table 2 Selected efficacy results, Merck Protocol 004 (ZVx vs. placebo, 3 years)

Outcome measure	PBO	ZVx	RRR	95% CI
Burden-of-illness score	5.68	2.21	61.1%	51.1–69.1
Incidence of PHN (per 1000 person-yr)	1.38	0.46	66.5%	47.5–79.2
Incidence of herpes zoster (per 1000 person-yr)	11.12	5.42	51.3%	44.2–57.6

ZVx was also superior to placebo in terms of the duration of postherpetic neuralgia (20 vs. 22 days; $p < .001$ for modified intent-to-treat (mITT) analysis).⁶

The results for mortality, serious morbidity, overall hospitalizations, zoster-related hospitalizations, use of pain medications, and interference with activities of daily living showed no significant treatment differences.

At this time, the durability of the vaccine is unclear and is undergoing further investigation in a follow-up, persistence substudy of the SPS. According to FDA analyses, there was a trend of decreasing efficacy in all three primary efficacy measures over time (the first 3 years after vaccination). Data beyond 3 years was difficult to interpret because relatively small numbers of participants with follow-up data were available. The need for revaccination has not been established.

Age, which was the most consistently and strongly associated factor explaining vaccine response, showed an apparent inverse relationship with ZVx efficacy. The relative decrease in the incidence of HZ was 63.9% in the 60 to 69-year old subgroup as compared with 37.6% in the ≥ 70 -year old subgroup. The corresponding relative decreases in BOI scores were 65.5% and 55.5%. However, the decrease in the incidence of postherpetic neuralgia was comparable in the 60 to 69 year and ≥ 70 year age strata (65.6% and 66.8%). Older participants (≥ 70 years) had higher rates of HZ and lower ZVx efficacy (38%) in prevention of HZ, as compared with younger participants 60 to 69 years of age (64%). There seems to be minimal ZVx efficacy in preventing HZ in participants over 75 years of age (37%) and vaccine efficacy was only 18% in participants over age 80 years (18%); however, the numbers of participants and HZ events were relatively small in the older age groups and these efficacy rates are based on post hoc analyses and are therefore inconclusive. It is notable that in post hoc analyses of safety data, the older age groups also had a numerically higher rate of serious adverse events in the Adverse Event Monitoring Substudy (see *Deaths and Other Serious Adverse Events*). It is noteworthy, however, that vaccine efficacy for the two pre-specified co-primary endpoints (HZ BOI and Incidence of PHN) were maintained above the pre-specified minimal criteria for success in the two pre-specified age strata, and the two-thirds reduction in the incidence of PHN was undiminished in the older age stratum.

According to FDA analyses of data from participants who developed herpes zoster rash, there was no significant difference between ZVx and placebo in the incidence of PHN occurring or persisting at 90 days after rash onset (8.6% vs. 12.%; $p = .08$) and in the BOI (82.50 vs. 87.75; $p = .25$). Reduction in the incidence of herpes zoster (51.3%) was the major treatment effect observed in the SPS. The incidence of postherpetic neuralgia and BOI scores added little additional information as efficacy measures.

It should be noted, however, that the FDA's conclusion (that the incidence of PHN and BOI scores added little information) was based on posthoc analyses of selected data and ignored the study purpose and pre-specified, FDA-approved study end points. It may be true that the

reduction in the HZ BOI and in the incidence of PHN are driven largely by a reduction in the incidence of HZ *in the younger age strata*. However, the results suggested that *in the older age strata* (≥ 70 years of age) the vaccine efficacy for HZ BOI and for the incidence of PHN were driven largely by a *reduction in the severity of HZ* in vaccinated participants. Moreover, efficacy for PHN was undiminished in the older age strata, in whom vaccine efficacy, as measured by the incidence of HZ, was diminished considerably. The burden of illness due to HZ-associated pain and discomfort and the incidence of PHN are considered to be the two manifestations of HZ that matter most to persons ≥ 60 years of age in whom ZVx was evaluated.

Immune responses (VZV antibody titer on glycoprotein ELISA [gpELISA]) observed after naturally occurring herpes zoster were larger relative to those seen after ZVx. The clinical relevance of the greater immune response, in terms of risk and severity of subsequent skin eruption from naturally occurring herpes zoster in comparison with post-ZVx herpes zoster, is unclear. Although titers of antibody to VZV increase in response to the exposure to VZV that results from HZ or vaccination, it is VZV-specific cell mediated immunity that limits the occurrence of HZ.

The durability of immune responses decreases, starting at about 6 months postvaccination, but remains above baseline values thereafter.

The date of last contact was not recorded for 99% of participants who had direct contact with study personnel and were not identified as deceased, lost to follow-up, or dropouts.

The VZV-specific antibody measured by gpELISA is known to be T-cell–dependent and is therefore considered by the manufacturer to reflect cellular immune response. Previous studies performed by the manufacturer showed that VZV-seronegativity is very rare among individuals over 30 years old, and only a small number of VZV-seronegative individuals have been identified and enrolled in clinical trials. Based on these previous findings, screening or otherwise assessing prevaccination immune status in individuals who are candidates for vaccination is felt to be unnecessary. In the SPS, relatively high levels of preexisting VZV immunity were observed even at baseline (prevaccination), and no seronegative individuals were seen among the 1395 participants included in the Cell-mediated Immunity Substudy. The gpELISA and VZV interferon-gamma assays were shown to *correlate* with protection; however, no specific value in either assay could reliably predict whether an individual is protected from HZ.

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 17).

Adverse Events (Safety Data)

According to the FDA, the safety population consisted of about 21,000 participants, including 19,270 participants who received ZVx 22,000 to 62,500 PFU per 0.5-ml in VA CSP #403 / Merck Protocol 004 and 698 participants who received ZVx 207,000 or 58,000 PFU per 0.65-ml dose in Protocol 009. Included in the safety dataset were 601 participants with Day 42 Automated Telephone Response System (ATRS) safety data (9% of the 6616 participants who participated in an Adverse Event (AE) Monitoring Substudy (1.6% of 38,546 total participants) in VA CSP #403 / Merck Protocol 004. Longer-term safety data was also passively collected from Day 43 postvaccination to end of study from 15,915 ZVx and 15,992 placebo recipients from the routine safety monitoring cohort, of which 3342 ZVx and 3268 placebo recipients were included in the AE Monitoring Substudy.

Day 42 Safety Follow-up (VA CSP #403 / Merck Protocol 004)

According to information provided by the sponsor to the FDA, adequate safety follow-up did not require participation in the planned Day 42 safety follow-up of VA CSP #403 / Merck Protocol

004. The sponsor used a hierarchical approach for consideration of complete safety follow-up not described in the protocol.

The safety dataset was obtained from several participant cohorts: 55% of all study participants who reported postvaccination adverse events around day 42 through an Automated Telephone Response System (ATRS), 11% of participants who reported adverse events over the 4 years following vaccination, and 1240 additional reports, some of which were added several years after vaccination, from participants already accounted for in the safety dataset. No information on reporting rates was available for monthly ATRS contacts (used to identify potential cases of herpes zoster and provide safety data in the Adverse Event Monitoring Substudy), or by baseline participant characteristics, by month, by site, or by study outcomes.

On December 15, 2005, the FDA clinical reviewer concluded that, because of the deficiencies in ATRS follow-up in VA CSP #403 / Merck Protocol 004, it was difficult to make conclusions about the relative safety of ZVx (0.5 ml).

Overall Adverse Events

The percentage of participants who experienced at least one AE was 1929/3345 (58.1%) in the ZVx group and 1117/3271 (34.4%) in the placebo group ($p < 0.05$) of the AE Monitoring Substudy. Most of these AEs were nonserious and most of the difference between the vaccine and placebo recipients was due to injection site AEs, which were generally mild and transient

Deaths and Other Serious Adverse Events

In VA CSP #403 / Merck Protocol 004, there was no safety pattern with respect to postvaccination deaths, hospitalizations, or serious adverse events (SAEs). Most SAEs leading to death were cardiovascular in both treatment groups. A wild-type strain was identified in all of the cases in which VZV DNA was detected by PCR from suspected HZ lesions; none of the cases were positive for Oka/Merck VZV.

In the AE Monitoring Substudy, the rates of SAEs reported to occur within 42 days postvaccination were significantly higher, 64/3345 (1.92%), in ZVx recipients as compared with 41/3271 (1.26%) in placebo recipients ($p < 0.05$). Older participants (≥ 70 years) had a higher rate of SAEs on ZVx (2.63%) versus placebo (1.49%). Rates of SAEs were also slightly higher in the ZVx group versus the placebo group in both genders. A similar pattern of higher rates of SAEs in the ZVx group was not observed in the Routine Safety Monitoring Cohort (see Table 4, page 12). The clinical relevance of the different patterns of SAE rates in the different cohorts is unclear. Overall, the rates of SAEs were similar on ZVx (1.37%) and placebo (1.36%).

In post hoc analyses of data from the routine safety monitoring cohort, SAEs were observed in 1.1% of participants age 60 to 69 years, 1.6% in participants 70 to 79 years, and 2.2% of participants age 80 and older. In the AE Monitoring Substudy, SAEs were experienced in 1.1% of participants 60 to 69 years of age, 2.2% in participants 70 to 79, and 5.1% in participants 80 and older.

Cardiovascular SAEs occurred in a numerically—not statistically—higher percentage of participants on ZVx (0.6%) than placebo (0.4%). No body system, clinical syndrome, or diagnosis was responsible for the group difference, and no temporal clustering of SAEs were seen relative to ZVx.⁹ The difference was attributed to chance. Currently, there is no evidence that the difference was due to ZVx.

Adding support to the safety of ZVx was the low number (5 of 31,925 vaccinees) of possibly vaccine-related SAEs (2 on ZVx and 3 on placebo (including 1 SAE reported on placebo on day 53 postvaccination). The manuscript writing committee also found no clinically meaningful differences between groups in the pathophysiology, nature, timing, intensity, or outcome of the

events in a post-hoc case-by-case review of the substudy SAEs.⁵ There were no significant differences in the incidence of hospitalizations; however, the hospitalizations were reported for a different time frame (day of vaccination to end of study). The FDA Vaccines and Related Biological Products Advisory Committee gave a qualified vote in favor of the evidence of ZVx safety and requested further information on the SAEs from the manufacturer.

Similarly, in Protocol 009, the results showed no specific pattern of SAEs, except more SAEs were observed in the high-dose group than in the low-dose group (4 versus 1, respectively).

There were no reports of disseminated VZV infection due to unmasking of an undiagnosed immunodeficiency.

Common Adverse Events

Injection site reactions. In VA CSP #403 / Merck Protocol 004, adverse events at injection-sites occurred at a higher rate on vaccine than placebo (48% vs. 17%), mainly because of increases in solicited injection-site adverse events such as erythema, pain/tenderness, and swelling. A relatively small but statistically significant ($p < 0.05$) increase in varicella-like rash at the injection site was seen in the ZVx group compared with the placebo group (20/19,270 [0.1%], vs. 7/19,276 [0.04%], respectively). The rates of herpes-zoster-like rash (17 [0.1%] vs. 36 [0.2%]) and confirmed cases of herpes zoster (7 [$< 0.1\%$] vs. 24 [0.1%]) were also decreased to a relatively small but statistically significant ($p < 0.05$) degree in ZVx versus placebo recipients. Most of the injection-site AEs were rated mild and resolved by day 4. A greater proportion of vaccine-treated than placebo-treated participants reported injection site reactions that were unsolicited, including pruritus, swelling, and warmth. The reports of injection site reactions were more common among females (vaccine and placebo recipients, respectively: 40% to 50% and 5% to 10%) than males (15% to 25% and 4% to 8%) as well as among the younger subgroup (60- to 69-year old) (30% to 43% and 5% to 10%) than the older subgroup (≥ 70 year old) (20% to 30% and 4% to 7%). All injection-site AEs were considered vaccine-related, regardless of the investigator's assessment of causality.

In Protocol 009, both the higher ZVx dose (207,000 PFU), relative to the lower dose (58,000 PFU), and the younger subgroup (50 to 59 years old), relative to the older subgroup (≥ 60 years old), were associated with higher rates of solicited and nonsolicited vaccine-related injection site reactions. Few of these reactions were rated as severe.

Other Adverse Events

Systemic reactions. In VA CSP #403 / Merck Protocol 004, the most common nonsolicited systemic adverse events were headache, respiratory infection, and rash ($\geq 2\%$ in at least one vaccination group). Vaccine-related fever, diarrhea, headache, and maculopapular rash were numerically more common in ZVx versus placebo recipients (all $< 1.5\%$). There was no significant treatment difference in the rates of systemic vaccine-associated adverse events. It should be noted that the vast majority of non-injection-site AEs were considered to be unrelated to vaccine by the investigator. In Protocol 009, the rate of systemic vaccine-related adverse events did appear to be higher in the higher dose group. The younger subgroup rated more specified systemic adverse events (e.g., headache) as severe.

Vaccine-induced HZ. No vaccine virus DNA was detected among approximately 919 participants who developed HZ for whom there was PCR assay data ($> 93\%$ of the evaluable cases of HZ, all of whom had wild-type VZV detected in rash specimens). Furthermore, in the 30 days following vaccination, there were 24 confirmed cases of HZ in the placebo group, but only 6 in the vaccine group. These data indicate that the ZVx did not induce or cause HZ.

It should be noted, however, that *varicella* vaccination in children has been associated with development of HZ lesions containing the Oka/Merck virus, in cases where HZ occurred at least 2 weeks after vaccination.^{11,12} This is because in VZV-susceptible persons who receive varicella vaccine, the vaccine virus established latency in sensory ganglia. However, information available to date indicates that the incidence of HZ following vaccination is lower than that following natural infection.

Day 43 to End of Study Safety Follow-up

At study termination (VA CSP #403 / Merck Protocol 004), about 2 to 5 years postvaccination, 99% of participants could be accounted for as either directly contacted by study personnel or confirmed as deceased. Participants who dropped out or were lost to follow-up amounted to less than 0.7% of the total study population.

The only systemic AE showing a statistically significant treatment difference was headache.

Since the safety data was passively collected and the nature of the safety data collected was inconsistent, the FDA clinical reviewer considered interpretation of the data to be limited.

Tolerability

There were no significant differences in the rates of discontinuations due to AEs. No participants in either treatment group discontinued because of vaccine-related AEs.

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 17).

Contraindications

History of anaphylactic / anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine.

History of primary or acquired immunodeficiency states including leukemia; lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system; or AIDS or other clinical manifestations of infection with human immunodeficiency viruses.

Immunosuppressive therapy, including high-dose corticosteroids.

Active, untreated tuberculosis.

Women who are or may be pregnant.

Warnings

Vaccine-associated rash or disseminated disease. Immunosuppressed individuals may be at risk of developing vaccine-associated rash or disseminated disease when vaccinated with a live attenuated vaccine, such as ZVx. ZVx has not been evaluated in individuals receiving immunosuppressive, daily topical or inhaled corticosteroid, or low-dose oral corticosteroid therapy.

Neomycin hypersensitivity. ZVx contains trace quantities of neomycin. Individuals with neomycin allergy often develop contact dermatitis, which is not a contraindication to receiving ZVx. Individuals who have a history of anaphylactic reaction to neomycin (topical or systemic preparations) should not receive ZVx.

Not for pediatric use. ZVx is not a substitute for pediatric Varicella Virus Vaccine Live (Oka/Merck; VARIVAX), used for prevention of varicella (chicken pox), and should not be used in children.

Precautions

Have adequate treatment provisions available for immediate use in case of anaphylactic / anaphylactoid reaction.

Consider deferral of vaccination during acute illness (e.g., fever > 38.5°C (> 101.3°F)).

The duration of protection from HZ beyond 4 years after vaccination with ZVx is unknown. The need for revaccination has not been defined.

The use of ZVx in individuals with a previous history of HZ has not been studied.

Transmission of vaccine virus may occur rarely between vaccinees who develop a varicella-like rash and susceptible contacts. Transmission of vaccine virus from vaccinees without a varicella-like rash has been reported but not confirmed. Weigh the risk of transmission of the attenuated virus to a susceptible contact against the risk of developing natural zoster that could be transmitted to a susceptible individual.

Based on postmarketing experience with varicella vaccines, the transmission of vaccine virus may occur rarely between vaccinees who develop a varicella-like rash and susceptible contacts.

Drug Interactions

Concurrent administration of ZVx and antiviral medications or other vaccines has not been evaluated. There is no specific guidance on the minimal interval to allow between administration of ZVx and antiviral agents or other vaccines.

Pregnancy and Nursing

Category C. ZVx should not be administered to pregnant females. Pregnancy should be avoided for 3 months after vaccination. Report any exposure to ZVx during pregnancy to (800) 986-8999.

It is not known whether VZV is secreted in human milk. Use caution if ZVx is administered to a nursing woman.

Geriatric Use

In the SPS (N = 38,546), the median age of enrolled participants was 69 years (range, 59 to 99 years). Of the 19,270 ZVx recipients, 10,378 were 60 to 69 years old; 7,629 were 70 to 79 years old; and 1,263 were 80 years of age or older.

Please consult the full product information on ZVx for additional precautions and other information.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on phonologic and orthographic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name *zoster vaccine live*: **Zoladex, Zorbitive, Zovirax**

LA/SA for trade name Zostavax: **Varivax, Zenapax, Zovirax, YF-Vax**

Two other possible look-alike/sound-alike errors may result from confusion with the **pediatric varicella virus vaccine live (Oka/Merck)** containing a lower concentration of VZV and the **varicella-zoster immune globulin (VZIG)**. Other product names containing “vaccine live” may be potential sources of medication confusion.

Data Compilation Tables

The numbers-needed-to-vaccinate based on incidence rates and prevalence rates of HZ and PHN are shown in Table 3, and the numbers-needed-to-vaccinate for major harm (i.e., SAEs) based on the total population and the AE Monitoring Substudy are shown in Table 4.

Table 3 Number-needed-to-vaccinate for benefit over 3.1 years, prevention of herpes zoster and postherpetic neuralgia

Parameter	Outcome based on prevalence (n/N (%))	
	HZ	PHN
Participants with outcome on ZVx,	315/19254 (1.64%)	27/19254 (0.14%)
Participants with outcome on Placebo	642/19247 (3.34%)	80/19247 (0.42%)
Treatment duration / follow-up	3.1 y	3.1 y
Relative Risk Reduction (95% CI)	51.0% (25.2–67.8)	66.3% (–33.8–91.5)
Absolute Risk Reduction (95% CI)	1.7% (0.7–2.7)	0.3% (–0.1–0.6)
p-value	0.001	0.188
NNVB (95% CI)	59 (37–143)	NSD [†]

NNVB, Number-needed-to-vaccinate for benefit

[†] If the absolute benefit of 0.3% is considered to be clinically relevant, although not statistically significant, the calculated NNVB for prevention of PHN would be 363 (95% CI: 167 to 1000)

Table 4 Number-needed to-vaccinate for harm, serious adverse events

Parameter (Population)	Outcome	
	SAEs (Total Population)	SAEs (AE Subpopulation)
Participants with outcome on ZVx, n/N (%)	255/19,270 (1.4)	64/3345 (1.9)
Participants with outcome on Placebo, n/N (%)	254/19,276 (1.4)	41/3271 (1.3)
Treatment duration / follow-up	42 d (0.11 y)	42 d (0.11 y)
Relative Risk Increase (95% CI)	0	52.6% (3.4–125.3)
Absolute Risk Increase (95% CI)	0	0.7 (0.1–1.3)
P-value	> 0.05	0.04 [†]
NNVH (95% CI) 42 d postvaccination	NSD	152 (77–1000)

NNVH, Number-needed-to-vaccinate for harm

[†] The statistically significant difference in SAEs was considered to be due to chance by the manufacturer since there was no clinical pattern to support a treatment difference.

Assessments of relative risks versus benefits was limited by differences in observation periods and lack of incidence rates for SAEs. The number-needed-to-vaccinate for benefit suggests that 59 (95% CI: 37 to 143) individuals would need to be vaccinated to prevent HZ in one additional person over a 3-year period. The NNVB for prevention of PHN did not reach the level of statistical significance (possibly because the incidence considered was in participants who developed HZ and not in the entire population, which would be the appropriate figure); however, the incidence of PHN was reduced by 66.5 % and duration of clinically significant pain in participants who developed HZ was reduced by 2 days.

Acquisition Costs

ZVx will be available in two package sizes at the Federal Supply Schedule (FSS) prices shown in Table 5.

Table 5 FSS acquisition costs for zoster vaccine

Dose	Package size	Cost/Package (\$)	Cost/Dose (\$)
≥ 19,400/ 0.65 ml	Single dose	113.75	113.75
	Ten (10) doses	1084.12	108.41

Pharmacoeconomic Analysis

Estimates of VHA pharmacy budget impact

The estimated lower and upper drug acquisition cost limits for ZVx were derived from the number of prescription recipients and number of VHA enrollees, respectively. Based on the number of prescription recipients aged 60 and older recorded in the VHA database for the 6-month period from September 2005 to February 2006, 62.5% (2,485,965/3,975,863) of veterans would meet the age criterion (60 years and older) for receiving zoster vaccine. This percentage was applied to the projected total numbers of unique prescription recipients and VHA enrollees in FY06 through FY08 to calculate the potential number of veterans, at the lower and upper limits, respectively, who may be eligible for vaccination with ZVx. Both the lower and upper cost limits consist of a range of the total number of individuals within the criteria-defined age range (upper range limit) and the number in the age range who would not be prescribed systemic antineoplastic and systemic glucocorticoid agents (lower range limit).

Drug acquisition costs would be counterbalanced by potential cost savings resulting from reduction in the costs to treat HZ and PHN—as well as to evaluate misdiagnosed prodromal symptoms of HZ—in those veterans who benefit from vaccination.

The vaccination cost would be equivalent to \$6549 for each individual who benefits (HZ prevention).

Estimated Lower Cost Limit (Based on Prescription Recipients)., The cost of ZVx over a 3-year period would be over \$390 million to prevent HZ in 59,651 pharmaceutical beneficiaries (and to prevent PHN in 9695 beneficiaries, if the absolute benefit for PHN prevention is considered to be clinically, although not statistically, significant) (Table 6).

Table 6 Costs of Zoster Vaccine to VA projected over a 3-year period (FY06–FY08)

Criteria (age in years)	No.	%	Cost†	Estimated No. Benefiting‡	
				HZ	PHN
Lower Estimate (New Uniques)					
Total Uniques over 3 years	5,628,706	100.0			
Age ≥ 60	3,519,429	62.5	\$390,656,569	59,651	9,695
Age ≥ 60 w/o SAN or SGC	3,333,322	59.2	\$369,998,780	56,497	9,183
Upper Estimate (New Enrollees)					
Total enrollees over 3 years	8,562,987	100.0			
Age ≥ 60	5,354,129	62.5	\$594,308,367	90,748	14,750
Age ≥ 60 w/o SAN or SGC	5,071,005	59.2	\$562,881,539	85,949	13,970

Total uniques in FY03: 4,017,776. New uniques in FY04 and not in FY03: 652,807. New uniques in FY05 and not in FY03 and FY04: 507,329. Percentages of participants within age groups were based on 6-month period from September 2005 to February 2006

SAN, Systemic antineoplastic (AN100–AN600, AN900); **SGC**, Systemic glucocorticoid (HS051)

† Calculated using \$111 per dose, average FSS cost as of 26 May 2006.

‡ NNVB = 59 for prevention of HZ over 3.1 years. NNVB = 363 for prevention of PHN if the absolute benefit based on prevention of PHN is considered to be clinically, although not statistically, significant.

If those veterans age 60 years and older with prescription records for systemic antineoplastics and systemic glucocorticoids are excluded, then 59.2% of beneficiaries would meet criteria for vaccination, and the 3-year cost would be over \$369 million to prevent HZ in 56,497 pharmaceutical beneficiaries (and prevent PHN in 9,183 beneficiaries, if the absolute benefit is considered to be clinically, but not statistically, significant).

Estimated Upper Cost Limit (Based on VHA Enrollees). The number of veterans not entered in the prescription database who are eligible for health care benefits and who will seek vaccination with ZVx are unknown. The projected number of VHA enrollees aged 60 years and older who could present for ZVx is 5,354,129 (all new enrollees) and the number who will not be prescribed immunosuppressants or systemic corticosteroids is 5,071,005. Using these figures, the range for the estimated upper cost limit would be over \$562 to \$594 million.

Model-based vaccine cost-effectiveness and cost-utility analyses

No comprehensive, VA-specific pharmacoeconomic analysis of ZVx is available.

Models of vaccine efficacy: Role of vaccination in preventive care in the UK

Vaccination of the elderly to prevent herpes zoster and postherpetic neuralgia is expected to be cost-effective under most scenarios and more favorable in older age groups because the burden of illness increases with age.¹⁴ Using three vaccine efficacy models and estimates of age-related risk of HZ (shingles), UK investigators showed that a single vaccination policy at age 65 years was the most beneficial option in both males and females.¹⁵ If a two-age vaccination policy at age 50 and 70 years were used, the number of cases saved would be improved over a single-age policy at a cost increase of 30% per case saved. Vaccination at age 50 and 70 years was potentially better than vaccination at age 45 and 65 years.

Conclusions

On December 15th, 2005, the FDA Vaccines and Related Biological Products Advisory Committee agreed that there was sufficient evidence of efficacy (incidence of HZ) only for the 60- to 80-year age group. With the qualification that the manufacturer provide

additional information on SAEs, they agreed there was sufficient evidence of safety in the same age group. The committee recommended full efficacy trials in individuals 50 to 59 years old.

The evaluation of ZVx remains to be completed, specifically in regard to the possibly higher risk of SAEs observed in the vaccine group and to cost-effectiveness evaluations.

ZVx is the only agent shown to prevent HZ. ZVx was associated with moderate to large *relative* reductions in the incidence of HZ and PHN, while the numerical, absolute reductions were somewhat small but perhaps acceptable for preventive therapy. A significantly higher rate of serious adverse events was observed on ZVx versus placebo in the 17% of study participants enrolled in an AE Monitoring Substudy. This difference was attributed to chance, and safety assessment results from the entire study population did not reveal any excess of SAEs in the vaccine group compared with the placebo group. Nevertheless it is important to verify this safety assessment with data from the SPS, since it is doubtful that a second large well-designed placebo-controlled trial will be performed.

Assessments of the value of ZVx in the VHA or a VHA public health vaccination program should take into consideration the likelihood that the incidence of HZ may increase in older adults as a result of loss of exposure to varicella, which is known to boost VZV-specific cell-mediated immunity (due to varicella vaccination of children). Because of the loss of this natural immunologic boosting to anti-VZV immunity in the newly aging population, it is possible that ZVx may have a greater effect in preventing HZ than that estimated in the major efficacy trial. VHA administrators should also consider that prevention of HZ and its complications, such as PHN, may have profound benefits at the individual level.

Questions that remain to be answered include (1) can the decrease in vaccine efficacy over time be minimized with booster doses; (2) can vaccine efficacy in older adults (≥ 70 years) improve with administration of higher doses without compromising safety; (3) what are the upper and lower age limits at which ZVx will confer significant benefits and be cost-effective in the prevention of herpes zoster and postherpetic neuralgia; and (4) are there differences in ZVx safety or efficacy based upon race.

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to August 2004) and OVID's Cochrane Central Register of Controlled Trials using the search terms herpes zoster, shingles, postherpetic neuralgia, vaccine and Zostavax. The search was limited to studies performed in humans, adults (19+ years), and published in English language. Reference lists of review articles were searched for relevant clinical trials. All randomized controlled trials, cohort, case-control, systematic reviews/meta-analyses comparing zoster vaccine with placebo or active comparator agent were included. The FDA Web site was also searched for clinical reviews on zoster vaccine. Since zoster vaccine was not FDA-approved at the time of monograph preparation, an AMCP dossier was not requested from the manufacturer.

Appendix Table 1 Overview of Zoster Vaccine Clinical Trials

Protocol	001	002	003	VA CSP#403 / Merck 004	005	007	009
Total Participants, N	276	398 (Dose 1) 206 (Dose 2)	21	38,546	196	210	698
ZVx Recipients, N	241	398	18	19,270	196	210	698
Population	Adults Healthy, seropositive	Adults Healthy, DM, or COPD, hx of varicella	Adults Healthy, low (≤ 5 gpELISA units/ml) or undetectable varicella-zoster virus antibody titer Central and S. America and Philippines	Adults ≥ 60 y old Healthy	Adults Healthy, history of varicella, previous 1–2 doses ZVx	Adults ≥ 60 y Healthy	Adults ≥ 50 y Healthy
Age Strata (N)	60–75 y (144) ≥ 76 y (132)	60–75 y ≥ 76 y	≥ 30 y (21)	60–69 y (20,747) $\geq 70–79$ y (15,197) ≥ 80 y (2602)	61–89 y	None	50–59 y ≥ 60 y
No. of Doses	1	2	1	1	1	2	1
Schedule (mo)	0	0 and 18	0	0	0	0 and 1.4	0
Dose (PFU)	Placebo 2,000 17,000 (aged) 19,000 34,000 67,000	Dose 1: Placebo 34,000 50,000 Dose 2: 50,000	50,000	Placebo 22,000–63,000 Includes aged lots	50,000	25,550	58,000 207,000
Efficacy	—	—	—	Yes (HZ) ~2 to 4.5 y	—	—	—
Safety (42 d)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Immunogenicity	Yes	Yes	Yes	Yes (≤ 3 y)	Yes (42-d-2-y)	Yes	Yes
Results available in FDA clinical briefing document	No	No	No	Yes	No	No	Yes

Adapted from Zostavax™ FDA Clinical Briefing Document⁶
Additional Sources: Zostavax FDA Clinical Briefing Document slides⁷; Oxman (2005)⁵

Appendix Table 2 Summary of Major Efficacy Trial

Citation	Oxman (2005) ⁵ , Zostavax FDA Clinical Briefing Document ⁶ and FDA Statistical Review and Evaluation of Zostavax ⁸ VA CSP #403, Merck Protocol 004 (from November 1998 to April 2004) Shingles Prevention Study, VA Cooperative Study #403
Study Goals	To demonstrate the safety and efficacy of a single 0.5-ml dose of zoster vaccine (ZVx) (i.e., varicella virus vaccine live (Oka/Merck) [Zostavax]) in persons aged 60 years and older to prevent herpes zoster (HZ), postherpetic neuralgia (PHN), and the burden of illness due to HZ-associated pain as measure by the burden-of-illness (BOI) score
Methods	<p>Study Design 22 MC DB PC Phase III RCT; unblinded vaccine technicians reconstituted and administered doses N_R = 38,546; N_A = 38,501 Participants stratified by study site and age 60–69 y and ≥ 70 y</p> <p>Interventions ZVx 22,000–63,000 PFU/0.5 ml s.c. single dose [per Oxman, 2005: 18,700–60,000 PFU/dose; median potency 24,600 PFU] Placebo (visibly distinct from ZVx)</p> <p>Allowed co-medications Famciclovir, APAP, NSAIDs, opioids, topical anesthetics</p> <p>Data Analysis mITT (excluded participants who developed HZ or discontinued within 30 d) PEVs: Burden of illness (BOI) due to HZ, incidence of postherpetic neuralgia (PHN). Incidence of HZ was a secondary efficacy variable. Vaccine efficacy in terms of BOI (VE_{BOI}) was defined as the relative reduction in the BOI score; the pre-specified criteria for vaccine success required a VE_{BOI} point estimate of 47% or more and a lower limit of the 95% CI greater than 25%. For vaccine efficacy in terms of incidence of PHN (VE_{PHN}), the corresponding requirements were VE_{PHN} point estimate of 62% or more and 95% CI lower limit greater than 25%. PHN was defined as pain associated with HZ that was rated as 3 or more on a 0 to 10 scale (0 = No pain; 10 = Pain as bad as you can imagine), persisting or appearing more than 90days after onset of rash. The cutoff of 3 was chosen because scores less than 3 were not associated with significant impairment in quality of life or functional capacity. Vaccine efficacy in terms of incidence of HZ (VE_{HZ}) was calculated in a similar manner to that used for VE_{PHN} and a 95% CI lower limit greater than 25% was the requirement for efficacy.</p>
Criteria	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> – Age ≥ 60 y – Hx of varicella or long-term (≥ 30 y) residence in continental U.S. <p>Notable exclusion criteria:</p> <ul style="list-style-type: none"> – Immunosuppression resulting from disease, corticosteroids (except intermittent topical or inhaled, < 800 mcg/d beclomethasone dipropionate or equivalent), or other immunosuppressive/cytotoxic therapy [however, participants who developed immunosuppression after vaccination were continued in the study]. – Active neoplastic disease except local skin cancer or other malignancies that are stable in the absence of immunosuppressive/cytotoxic therapy (e.g., prostate cancer) – Significant underlying illness that would be expected to prevent completion of the study (e.g., expected survival not estimated to be at least 5 years) – Prior HZ or prior receipt of varicella vaccine – Allergic sensitivity to neomycin – Hx of anaphylactoid reaction to gelatin – Receipt of blood products within 3 months before randomization or planned during study period – Receipt of any other vaccines within 1 mo before study vaccination (2 wk for inactivated vaccines, such as influenza vaccine, or other nonreplicating vaccines, such as dT, pneumococcal, hepatitis A, hepatitis B vaccines) or scheduled within 6 wk of study vaccination – Receipt of antiviral therapy at the time of enrollment – Homebound or nonambulatory – Conditions that would interfere with evaluation of HZ or compliance with protocol requirements (e.g., chronic pain syndromes, cognitive impairment, severe hearing loss) or that might interfere with the interpretation of the study (e.g., urinary tract infection, influenza) – Premenopausal females

Zoster vaccine NMEM (Final 111606)

Updated version may be found at www.pbm.va.gov or vaww.pbm.va.gov

<p>Population Characteristics and Disposition</p>	<p>– Hx of recurrent herpes simplex virus, > 3 episodes per year, treated with episodic or daily antiviral therapy</p> <p>Age, median, y: 69 (both treatment groups) Age 60–69 y, n: 20,747; Age ≥ 70 y, n: 17,799 Age ≥ 80 y, %: 6.9% vs. 6.6% for placebo vs. ZVx Male/Female, n (%): 22,760 (59.0%) / 15,786 (41.0%) Race, n (%): White 36,774 (95.4%); Black 815 (2.1%); Hispanic/Other/Unknown 957 (2.5%) No / Mild health-related limitations: 51.3% / 38.6% Number of veterans was not recorded; however, 49% reported military service.</p> <p>Participant Disposition</p> <table border="1" data-bbox="472 470 1070 716"> <thead> <tr> <th rowspan="2"></th> <th colspan="2">PBO</th> <th colspan="2">ZVx</th> </tr> <tr> <th>N = 19276</th> <th></th> <th>N = 19270</th> <th></th> </tr> <tr> <th></th> <th>n</th> <th>%</th> <th>n</th> <th>%</th> </tr> </thead> <tbody> <tr> <td>Vaccinated</td> <td>19276</td> <td>100.0</td> <td>19270</td> <td>100.0</td> </tr> <tr> <td>Completed</td> <td>18357</td> <td>95.2</td> <td>18359</td> <td>95.3</td> </tr> <tr> <td>Discontinued:</td> <td>919</td> <td>4.8</td> <td>911</td> <td>4.7</td> </tr> <tr> <td> Died</td> <td>792</td> <td>4.1</td> <td>793</td> <td>4.1</td> </tr> <tr> <td> Withdrawn from study</td> <td>75</td> <td>0.4</td> <td>57</td> <td>0.3</td> </tr> <tr> <td> Lost to follow-up</td> <td>40</td> <td>0.2</td> <td>53</td> <td>0.3</td> </tr> <tr> <td> Other</td> <td>12</td> <td>0.1</td> <td>8</td> <td>0.0</td> </tr> </tbody> </table> <p>No information was available on the identity of participants who were enrolled in the pivotal study at VA Medical Center sites who were not eligible to receive VA Medical Center healthcare. Therefore it is impossible to determine whether differences in baseline participant characteristics or differential follow-up and access to healthcare information might impact on the reported safety and/or efficacy of ZVx.</p>		PBO		ZVx		N = 19276		N = 19270			n	%	n	%	Vaccinated	19276	100.0	19270	100.0	Completed	18357	95.2	18359	95.3	Discontinued:	919	4.8	911	4.7	Died	792	4.1	793	4.1	Withdrawn from study	75	0.4	57	0.3	Lost to follow-up	40	0.2	53	0.3	Other	12	0.1	8	0.0
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<p>Efficacy Results</p>	<p>Primary and Secondary Efficacy Results</p> <table border="1" data-bbox="472 961 1130 1161"> <thead> <tr> <th></th> <th>PBO</th> <th>ZVx</th> <th>PE</th> <th>95% CL</th> <th>P-value</th> </tr> </thead> <tbody> <tr> <td>N_R</td> <td>19,276</td> <td>19,270</td> <td></td> <td></td> <td></td> </tr> <tr> <td>N_A</td> <td>19,246</td> <td>19,254</td> <td></td> <td></td> <td></td> </tr> <tr> <td>BOI score</td> <td>5.68</td> <td>2.21</td> <td>61.1</td> <td>51.1, 69.1</td> <td>< 0.001</td> </tr> <tr> <td>PHN (i)</td> <td>1.384</td> <td>0.464</td> <td>66.5</td> <td>47.5, 79.2</td> <td>< 0.001</td> </tr> <tr> <td>HZ (i)</td> <td>11.12</td> <td>5.41</td> <td>51.3</td> <td>44.2, 57.6</td> <td>< 0.001</td> </tr> <tr> <td>DCSP (d)[†]</td> <td>22</td> <td>20</td> <td></td> <td></td> <td>< 0.001</td> </tr> <tr> <td>SOI</td> <td>180.5</td> <td>141.2</td> <td></td> <td></td> <td>0.008</td> </tr> </tbody> </table> <p>i, Incidence per 1000 person-years; N_A, Number of participants analyzed; N_R, Number of participants randomized; PE, Point estimate of difference in incidence rate (per 1000 person-years), ZVx vs. placebo [†] 24 and 21 d (p = 0.03) in published report; 22 and 19 d (p = 0.10 by log-rank, p = 0.04 based on protocol-specified age-stratified log-rank test) in statistical report.</p> <p>Overall, ZVx significantly reduced BOI scores (by 61.1%), incidence of PHN (by 66.5%), duration of clinically significant pain (DCSP) by 2 d, and severity of illness (SOI) scores (by ~39 points). There were 642 evaluable HZ cases in the placebo group and 315 in the ZVx group. The incidence of HZ was decreased by 51.3% from 11.12 to 5.41 per 1000 person-years. The crude HZ incidence rate was 3.34% on placebo and 1.64% on ZVx (PE = 51.0%; 95% CL: 44.0%, 57.1%). Vaccine efficacy based on HZ incidence met the pre-specified success criterion. The percentage of PHN among HZ cases was 12.5% (80/642) on placebo and 8.57% (27/315) on ZVx (p-value, Fisher = 0.08). The incidence of PHN was decreased by 66.5% from 1.384 to 0.464 per 1000 person-years with ZVx relative to placebo. VE_{PHN} was similar when PHN was defined using alternative cutoff times for pain duration/persistence. VE_{HZ} was 63.9% among younger participants and 37.6% among older participants (≥ 70 y) (p < 0.001).</p>		PBO	ZVx	PE	95% CL	P-value	N _R	19,276	19,270				N _A	19,246	19,254				BOI score	5.68	2.21	61.1	51.1, 69.1	< 0.001	PHN (i)	1.384	0.464	66.5	47.5, 79.2	< 0.001	HZ (i)	11.12	5.41	51.3	44.2, 57.6	< 0.001	DCSP (d) [†]	22	20			< 0.001	SOI	180.5	141.2			0.008	
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Durability of ZVx Efficacy				
Year	PE	95% CL		
HZ Incidence				
1	0.623	0.507, 0.714		
5	0.504	-1.324, 0.920		
PHN Incidence				
1	0.849	0.610, 0.954		
3	0.419	-0.344, 0.762		
5	0.007	-76.930, 0.987		
HZ Pain BOI				
1	0.794	0.682, 0.867		
5	0.748	0.190, 0.922		
Only selected time points shown.				
ZVx Efficacy by Age				
Age (y)	HZ Incidence (1000 person-years)		VE _{HZ} (95% CL)	
	PBO	ZVx		
Predefined Analysis				
60-69	10.79	3.90	0.64 (0.56, 0.71)	
≥ 70	11.50	7.18	0.38 (0.25, 0.48)	
Post hoc FDA Analysis				
			Calculated VE _{HZ}	
70-74	11.438	6.435	0.44	
75-79	11.312	7.182	0.37	
80-84	12.230	9.773	0.20	
85-89	11.570	10.040	0.13	
90+	14.286	19.608	-0.37	
VE _{HZ} , Vaccine efficacy, incidence of herpes zoster (PBO - ZVx) / PBO				
HZ Complications: no clear treatment differences in either common complications (eg., prodromal pain, acute pain, allodynia, pain 30 d after rash onset) or life-threatening complications (pneumonitis, cerebral dysfunction, meningoencephalitis).				
Placebo vs. ZVx:				
Use of antiviral medication: 85.7% vs. 87.3%				
Treatment initiated within 72 h of rash onset: 65.9% vs. 64.1%				
SF-12 Health Survey and EuroQoL Visual Analog Scale: No treatment differences				
Cell-mediate Immunity Substudy (gpELISA titers 6 wk postvaccination)				
	PBO		ZVx	
	Response	95% CL	Response	95% CL
Titer (units/ml)		n = 684		n = 667
% ≥200	64.6%	60.9%, 68.2%	83.4%	80.3%, 86.1%
GMT	291.4	269.3, 315.3	474.7	441.5, 510.5
Fold Rises vs. Day 0		n = 655		n = 673
GMFR	1.0	1.0, 1.0	1.7	1.6, 1.8
GMT, Geometric mean titer; GMFR, Geometric Mean Fold Rise				
The gpELISA titers persisted from Day 0 to 3years, albeit at decreasing levels over time. At 3 years, the geometric mean titer was 305.7 (95% CL, 280.6, 333.2) on placebo and 331.6 (95% CL: 305.1, 360.4) on ZVx. The corresponding geometric mean fold rise was 1.0 (1.0, 1.1) and 1.2 (1.1, 1.3) for placebo and ZVx, respectively.				
Prevaccination titers, age, and timing of the 6-wk blood sample had statistically significant effects on the gpELISA responses at 6 wk postvaccination. ZVx recipients with relatively lower gpELISA titers at Day 0 appeared to have relatively lower titers but higher folder rises at 6 wk postvaccination. Age was a more obvious response factor in the subgroup with the lowest prevaccination titers, with higher fold rises in the younger age group vs. the older age group when prevaccination titers were < 100 but similar fold rises when titers were ≥ 100.				

Safety Results		Safety follow-up via the Automated Telephone Reporting System suffered from a large amount of underreporting for reasons that were unclear.					
		ATRS Safety Follow-up at Day 42					
		ITT N = 38,546					
		n		%			
With data	25,613	66					
W/o data	12,994	34					
Any AE	174	0.5					
		From day 0 to end of study, the numbers and percentages of deaths were similar in both treatment groups of the total study population (data not shown here).					
		Clinical Adverse Events (days 0–42): Routine Safety Monitoring Cohort, FDA clinical review (contrast with Table 4 of published report)					
		PBO (N = 16005)		ZVx (N = 15925)			
Safety result		N	%	N	%		
W/safety follow-up	15468	96.6	15345	96.3			The 2 vaccine-related SAEs occurring in the ZVx group were polymyalgia and asthma. In the placebo group, the 2 vaccine-related SAEs were anaphylaxis and polymyalgia rheumatica.
SAE	213	1.38	191	1.24			
SAE-VxR	2	0.01	2	0.01			
Died	14	0.09	11	0.07			
WDAE	1	0.01	1	0.01			
WDAE-VxR	0	0.0	0	0.00			
		SAE, Serious adverse event; VxR, Vaccine-related; WDAE, Withdrawal due to adverse event					
		Clinical Adverse Events: Adverse Event Monitoring Substudy, FDA clinical review (contrast with Table 4 of published report)					
AE		PBO (N = 3271)		ZVx (N = 3345)		Diff in Risk	95% CL
Result		n	%	n	%		
<i>Day 0–End of Study</i>							
Hosp, HZ-related	6	0.2	5	0.2	-0.1 [†]	-0.7, 0.5	
<i>Days 0–42</i>							
W/safety follow-up	3249	99.3	3326	99.4			
≥ 1 SAE	41	1.26	64	1.92	0.7*	0.1, 1.3	
SAE-VxR	1	0.03	0	0.00	NR	NR	
Died	2	0.06	3	0.09	NR	NR	
WDAE	0	0.00	0	0.00	NR	NR	
WDAE-VxR	0	0.00	0	0.00	NR	NR	
≥ 1 AE	1117	34.4	1929	58.1	23.7	21.3, 26.0	
≥ VxR Systemic AE	160	4.9	209	6.3	1.4*	0.3, 2.5	
≥ 1 Inj site AE	539	16.6	1604	48.3	31.7	28.3, 32.6	
		* p < 0.05					
		† Risk calculated per 1000 person-years of follow-up					
		Inj, Injection; NR, Not reported; SAE, Serious adverse event; VxR, Vaccine-related; WDAE, Withdrawal due to adverse event					
		Of the total 30 deaths (14 on ZVx, 16 on placebo) occurring between day 0 and 42 postvaccination, none were considered to be related to study vaccine by investigators. According to the FDA clinical reviewer, it was difficult to draw conclusions from the deaths because most of them occurred in the more passively monitored Routine Monitoring Cohort.					
		In the routine safety monitoring cohort, SAEs were experienced by 1.1% of participants 60–69 years of age, 1.6% in participants 70–79, and 2.2% of participants age 80 and older.					

		Adverse event monitoring substudy by age				In the safety substudy, there was a 60% relative increase in SAEs (see table above) and an 80% increase in participants age ≥ 70 years. Additional details on these cases were requested by the FDA.
		PBO		ZVx		
AE Type		$N_s = 1709$ 60–69 y %	$N_s = 1540$ ≥ 70 y %	$N_s = 1726$ 60–69 y %	$N_s = 1600$ ≥ 70 y %	
SAE		1.05	1.49	1.27	2.63	
≥ 1 AE		37.7	30.7	65.0	50.5	
Inj site		19.1	13.8	56.6	39.2	
Systemic		25.2	22.0	26.1	23.1	
ZVx-related		21.9	17.2	58.3	41.2	

Inj, Injection; N_s , Number of participants with safety follow-up; SAE, Serious adverse event

In the AE Monitoring Substudy, SAEs were experienced in 1.1% of participants 60–69 years of age, 2.2% in participants 70–79, and 5.1% in participants 80 and older.

Cardiovascular events were reported as SAEs more frequently after ZVx than after PBO during day 0 to 42 postvaccination in the AE Monitoring Substudy. Overall cardiovascular events were reported as SAEs in 20 of 3326 ZVx recipients (0.6%) versus 12 of 3249 PBO recipients (0.4%). Coronary artery disease–related conditions (angina pectoris, coronary artery disease, coronary occlusion, cardiovascular disorder, myocardial ischemia, and myocardial infarction) occurred in 10 ZVx participants (0.3%) and 5 PBO participants (0.2%). The percentages of overall cardiovascular events (0.4%) and coronary artery disease–related conditions (0.2%) were the same for ZVx ($N = 18,671$) and PBO ($N = 18,717$) in the entire study cohort.

There was a greater risk of erythema, pain/tenderness, and swelling at the injection site on ZVx vs. placebo (all $p < 0.001$). These AEs were numerically greater in the younger age group (60 to 69 y) vs. the older age group (≥ 70 y), and among females compared with males. All of these injection-site AEs were specifically queried in the vaccine report card. NB: All injection-site AEs were considered vaccine-related, regardless of investigator assessment. This assumption may affect the overall rate of vaccine-related events.

Numerically higher rates of vaccine-related fever, diarrhea, headache, and maculopapular rash occurred on ZVx vs. placebo (all $< 1.5\%$). No statistically significant treatment differences were seen in the rate of systemic AEs. Most common nonsolicited systemic AEs: headache, respiratory infection, and rash ($\geq 2\%$ in at least one vaccination group).

Safety Data from Day 42 through End of Study (passive monitoring)
Automated Telephone Response System (ATRS)
 The proportion of participants with contact at each month overall and by site were not reported to the FDA, making it difficult to interpret the submitted safety data.
Routine Safety Monitoring Cohort
 Numerically lower rates of withdrawals due to adverse events and withdrawals due to serious adverse events were seen on ZVx (both 0.04%) vs. placebo (both 0.08%). ($N_s = 15,915$ and 15,992 for ZVx and placebo, respectively).
AE Monitoring Substudy
 Except for headache, no statistically significant treatment differences were seen in any reported vaccine-related systemic AEs

	<p>calculating the p-value of 0.008 for the contribution of HZ BOI beyond the HZ incidence. The test was based on a conditional subcohort that had a diagnosis of HZ, not the entire study population, and therefore the integrity of randomization was not applicable. However, the FDA clinical reviewer’s substitution of post hoc analyses and tertiary end points for the pre-specified and FDA-approved co-primary end points may have been inappropriate and may have not fairly and accurately reflected the results of the SPS.</p> <p>During the course of the study, the co-primary end point, PHN, was redefined as reduction in the incidence of PHN occurring or persisting at Day 90 rather than at Day 30 as originally planned. In the sponsor’s sensitivity analyses, if the original cut-off of 30 d (or 60 d) had been used, the results for PHN would have not met the success criterion (reduction in PHN > 62%).</p> <p>According to the FDA clinical reviewer, “it is not clear that a 90-day cutoff is the most appropriate in a preventive study which seeks to evaluate the overall BOI due to PHN experienced in the study population.”(Rohan, 2005 #4512) It should be noted that this change in the definition of PHN was made at the suggestion of the Data Safety and Monitoring Board of the SPS and approved by the FDA prior to unblinding in order to bring the definition of PHN for the primary efficacy analysis into conformity with current scientific and clinical practice.</p> <p>There were relatively fewer participants at the upper age range. Study excluded participants with common co-morbidities, which may have affected the efficacy and adverse event estimates. Inclusion of a relatively healthy study population may have limited the ability of the trial to determine whether ZVx affected rates of zoster-related hospitalization and other severe complications.</p> <p>Protocol-allowed use of concomitant antivirals may have decreased the rate of HZ complications.</p> <p>Safety data were incompletely reported to the FDA; therefore, it was difficult for the FDA reviewer to draw conclusions about the relative safety of ZVx.</p> <p>External validity to VA: Applicable to VA patients, although according to the study biostatistician (G. Johnson, e-mail communication, April 2006), only 49% of study participants reported military service and results are limited to the population studied (relatively healthy, ambulatory, age ≥ 60 years). There is extremely limited evidence of ZVx efficacy in minority populations, but no evidence to suggest it would be ineffective in these populations.</p> <p>Sponsorship: Supported by grants from Merck (to the VA Cooperative Program) and James R. and Jesse V. Scott Fund for Shingles Research. Merck participated in the planning of the trial. Merck developed and published the statistical methods for analyzing BOI before initiation of the trial.</p>
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Appendix Table 3 Summary of Major Safety Trial

Citation	Protocol 009, FDA Clinical Reviewer Briefing Document ⁶
Study Goals	To compare the safety and tolerability profile of a higher potency zoster vaccine (~207,000 plaque-forming units (PFU) / 0.65-ml dose) with that of the zoster vaccine at a lower potency (~58,000 PFU/0.65-ml dose) [to determine the safety of lots at the higher end of the potency range]. According to the FDA, the goal of this trial was to support an indication in persons 50 to 59 years of age and the use of a higher potency and volume (0.65 ml) dose of zoster vaccine (ZVx) (i.e., varicella virus vaccine live (Oka/Merck) [Zostavax]), and to evaluate vaccine safety.
Methods	<p>18 MC DB PC RCT, 42-day follow-up</p> <p>Participants stratified by age 50–59 y (n = 185) and ≥ 60 y (n = 513)</p> <p>Study end points: (1) vaccine-related serious clinical adverse events occurring Day 1 through Day 42 postvaccination; (2) composite end point of moderate or severe injection-site pain/tenderness/soreness or swelling occurring day 1 through Day 5 postvaccination in the higher potency vaccine group as compared with a historical adverse event rate for Pneumovax23TM</p> <p><i>Statistical considerations</i></p> <p>If the incidence rate of a serious adverse event was 0.47%, then there was an 85% chance of observing at least one such SAE.</p> <p>If there are ~400 participants in the higher potency group and ~200 participants in the lower potency group, and no SAEs were observed in both groups, then a test of risk difference between treatment groups (2-sided, 0.05 level) would provide 97.5% confidence that the true rate was < 0.92%.</p> <p>The study had ~85% power to detect a 7.4-percentage-point increase in adverse event incidence rates in the higher potency group from a hypothetical incidence rate of 5.0% in the lower potency group.</p> <p>Clinical significance for this end point was defined by the upper limit of the 95% CI for the observed incidence rate exceeding 21.5% (pre-established from past clinical experience with pneumococcal vaccine polyvalent, Pneumovax23).</p> <p><i>Interventions</i></p> <p>ZVx 207,000 PFU (N = 464)</p> <p>ZVx 58,000 PFU (N = 234)</p> <p>Single dose</p>

Criteria	<p><i>Enrollment criteria</i></p> <ul style="list-style-type: none"> - Adults ≥ 50 y - Healthy - Varicella history-positive - HZ history-negative - Females postmenopausal or with negative pregnancy test - No history of hypersensitivity reaction to gelatin, neomycin, or any component of the vaccine - No prior receipt of any varicella vaccine; no immune globulin and/or blood products within 5 mo prior to or expected during 42 d after vaccination - No live vaccinations within 6 wk prior and until 42 d after vaccination - No inactivated vaccinations within 7 d prior to and until 42 d after vaccination - No acute intercurrent illness or significant underlying illness; no immune dysfunction caused by a medical condition, use of immunosuppressive therapy, or any other cause; no concomitant use of antiviral therapy with activity against herpesviruses 																			
Population Characteristics	Not reported																			
Efficacy Results	Not applicable																			
Safety Results	<p><i>Deaths and Other Serious Adverse Events</i></p> <p>No deaths were reported. There were 4 SAEs in the higher potency group and 1 SAE in the lower potency ZVx group.</p> <p><i>Moderate–Severe Injection Site Reactions</i></p> <p>For moderate–severe injection-site reactions, the upper limit of the 95% CI of the incidence rate (21.0%) in the higher potency vaccine group was below the clinically meaningful limit (21.5%)</p> <p>Participants with Moderate–Severe Injection-site Reactions (Day 1–5 postvaccination)</p> <table border="1" data-bbox="475 867 1382 1129"> <thead> <tr> <th rowspan="2"></th> <th colspan="2">ZVx Higher Potency</th> <th colspan="2">ZVx Lower Potency</th> </tr> <tr> <th>n</th> <th>% (95% CL)</th> <th>n</th> <th>% (95% CL)</th> </tr> </thead> <tbody> <tr> <td>Moderate or severe injection-site pain/tenderness/soreness or swelling (> 2 inches at largest diameter)</td> <td>79</td> <td>17.2 (13.9, 21.0)</td> <td>21</td> <td>9.0 (5.6, 13.4)</td> </tr> <tr> <td>Difference (High – Low)</td> <td colspan="4">8.2 (95% CL: 2.9, 13.1)</td> </tr> </tbody> </table> <p>NS, Number of participants with safety follow-up</p> <p><i>Nonserious adverse events</i></p> <p>Rates of systemic and vaccine-related systemic adverse events were similar between treatment groups.</p> <p>Higher rates of solicited AEs (pain, tenderness, soreness, and swelling) and higher rates of nonsolicited AEs (pruritus, swelling, and warmth) were seen in the higher potency vaccine group. No severe local injection-site reactions were reported.</p> <p>Severe specific AEs were reported by no more than 1 lower potency ZVx participant, whereas severe headache occurred in 6 participants, severe arthralgias occurred in 2, severe upper respiratory infection occurred in 3, and severe nasopharyngitis occurred in 2 participants of the higher potency ZVx group.</p> <p>Less than 1% of participants in both treatment groups developed a temperature > 101°F.</p> <p>No varicella-like rashes with > 100 lesions were reported. Three HZ-like rashes were reported in each treatment group. No cases of Oka/Merck virus were detected (using PCR) from varicella- or HZ-like rashes.</p> <p><i>Age-related Safety Effects</i></p> <p>Among younger participants (age 50–59 years), the percentage of participants with at least 1 injection-site AE was numerically higher (82.9%) in the higher potency ZVx group than the lower potency group (69.4%). In comparison, among the older participants (age ≥ 60 years), the corresponding rates were similar (54.8% and 56.4%, respectively).</p>		ZVx Higher Potency		ZVx Lower Potency		n	% (95% CL)	n	% (95% CL)	Moderate or severe injection-site pain/tenderness/soreness or swelling (> 2 inches at largest diameter)	79	17.2 (13.9, 21.0)	21	9.0 (5.6, 13.4)	Difference (High – Low)	8.2 (95% CL: 2.9, 13.1)			
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Conclusions	<p>According to the FDA clinical reviewer, these study results are considered descriptive. They evaluate possible dose-response relationships of solicited and adverse events in general over the selected dose range. In general, younger participants (50–59 year old) had higher rates of vaccine-related AEs, and this age-related difference was more pronounced in the higher potency vaccine group.</p> <p>A trend of increased SAEs were seen in this trial and VA CSP #403 / Merck Protocol 004. In this trial, 4 participants (0.9%) of the higher potency ZVx group and 1 participant (0.4%) of the lower</p>																			

	<p>potency group reported SAEs. In VA CSP #403 / Merck Protocol 004, a trend of increased SAEs from Day 0 to 42 postvaccination was seen in the AE Monitoring Substudy, most notable in the ≥ 70-year-old cohort. The clinical relevance of these observations is unclear.</p>
<p>Critique</p>	<p>Strengths: Randomized safety study. Limitations: Only 185 participants between the ages of 50 and 59 years. This was insufficient evidence to establish safety in this age group. The usefulness of a 21.5% upper limit on the difference between percentage of participants in the high versus low potency ZVx groups with moderate or severe injection-site pain, tenderness, soreness, or swelling (> 2 inches diameter) based on historical experience with Pneumovax23 is unclear. Shorter-term (42-d) follow-up.</p> <p>External validity: Not evaluable</p> <p>Quality rating: Not evaluable</p>