Vaccines and Related Biological Products Advisory Committee

Meeting Date: December 15, 2005

FDA Clinical Briefing Document for

Merck & Co., Inc.
Zoster vaccine live (Oka/Merck)
Zostavax™

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1.0 General Information

Product name

Proper name:	Varicella Virus Vaccine Live (Oka/Merck)
Proposed trade name:	ZOSTAVAX™

Product composition:
ZOSTAVAX, manufactured at Merck & Co., Inc. (Merck), West Point, Pennsylvania, is a sterile lyophilized product prepared by formulating the attenuated Oka/Merck VZV strain (a live attenuated virus) propagated in MRC-5 cell culture. The drug product is stored at –15 °C until use and is reconstituted with sterile diluent just prior to use.

Merck intends that the licensed product will be a 0.65 mL dose formulation which when reconstituted as directed and stored at room temperature for up to 30 minutes, each 0.65-mL dose contains a minimum of 19,400 PFU (plaque forming units) of Oka/Merck varicella-zoster virus; 31.16 mg of sucrose, 15.58 mg of hydrolyzed gelatin, 3.99 mg of sodium chloride, 0.62 mg of monosodium L-glutamate monohydrate, 0.57 mg of sodium phosphate dibasic, 0.10 mg of potassium phosphate monobasic, 0.10 mg of potassium chloride; residual components of MRC-5 cells including DNA and protein; and trace quantities of neomycin, and bovine calf serum. The product contains no preservatives.

The virus seeds, drug substance process and varicella vaccine bulk used for ZOSTAVAX™ are the same as for varicella component in Merck's FDA licensed vaccines, VARIVAX™ and ProQuad™. The varicella component of these latter two vaccines is indicated for vaccination against varicella in individuals 12 months of age and older in the case of VARIVAX™ and in children 12 months to 12 years of age in the case of ProQuad®.

Products Used	
Manufacturer	Merck & Co., Inc.
Proposed indication	Immunization of adults ≥50 yrs for prevention of herpes zoster, postherpetic neuralgia and reduction of acute chronic zoster associated pain
Dosing regimen and Route of administration	Single dose, subcutaneously

PRINCIPAL CLINICAL STUDIES SUBMITTED IN SUPPORT OF LICENSURE AND LABELING

Protocol 004
This protocol was designed to demonstrate the safety and efficacy of a single 0.5 mL dose of ZOSTAVAX™ in persons aged 60 years and older to prevent herpes zoster (HZ), post-herpetic neuralgia (PHN) and the burden of illness due to HZ-associated pain as measured by the burden-of-illness (BOI) score.

Protocol 009
Protocol 009 was designed to support an indication in persons 50-59 years of age and use of a higher potency and volume (0.65 mL) ZOSTAVAX™ dose. Subjects were evaluated for safety.

Executive Summary:
This briefing document contains a summary of the safety, immunogenicity and efficacy data from Protocol 004 and safety data from Protocol 009 provided by Merck & Co., Inc. to support approval of their Varicella Virus Vaccine Live (Oka/Merck) (Trade name: Zostavax™), for single dose immunization of adults 50 years of age and older.

Efficacy Data – Protocol 004
The submitted efficacy data from pivotal Study 004 demonstrate that in a group of relatively healthy adults, aged 60 years and older, a single dose of ZOSTAVAX™ (22,000 – 62,500 pfu/dose) reduced the incidence of herpes zoster (HZ) by 51.3% (95% CIs 44.2, 57.6), the incidence of PHN by 66.5% (95% CIs 47.5, 79.2) and reduced the burden-of-illness (BOI) score, a composite measure of HZ pain incidence, severity and duration, by 61.1% (95% CIs 51.1, 69.1) when comparing rates by treatment groups over the first ~3 years following vaccination.

Statistically significant differences were demonstrated in the duration of post-herpetic neuralgia (20 days in the vaccine group vs. 22 days in the placebo group (p-value <0.001 for MITT, p-value = 0.041 for evaluable HZ).

No statistically significant vaccine effects were seen on the rates of mortality, hospitalizations (overall and zoster-related), serious morbidity, use of pain medications and interference with activities of daily living (ADLI) over the course of the study.

The study report shows a trend of decreasing efficacy in all three major efficacy endpoints (HZ incidence, PHN incidence and BOI) over the first 3 years following vaccination. Interpretation of data in later years, i.e., more than 3 years postvaccination, is limited by the relatively small proportion of subjects with follow-up.

Age appears to be an important factor in some study measures of vaccine efficacy: the incidence of HZ was reduced by 63.9% in subjects 60-69 years old and by 37.6% in those 70 years of age and older; and the BOI score was reduced by 65.5% in subjects 60-69 years old and by 55.5% in those 70 years of age and older. A similar reduction in PHN was seen in both ZOSTAVAX™ and placebo recipients in both age groups.

In FDA analyses of Study 004 data, the incidence of post-herpetic neuralgia occurring or persisting at 90-days following HZ rash onset was reduced from 12.5% in placebo recipients who developed HZ to 8.6% in vaccine recipients who developed HZ (p-value [Fisher's Exact = 0.08]. The median HZ BOI was 82.50 in vaccine recipients who developed HZ and 87.75 in placebo recipients who developed HZ (p-value (Wilcoxon) = 0.25). It appears that the major treatment effect in Protocol 004 is reflected by the decrease in the incidence of HZ (51.1%) and that the additional major efficacy endpoints, HZ BOI and incidence of PHN provide little additional information. Further information is contained in the FDA Statistical Reviewer's Briefing Document.

FDA analysis of the data further reveals a consistent trend toward progressive loss of vaccine efficacy in prevention of HZ with increasing age, although the numbers of subjects and cases of HZ occurring at the oldest ages are relatively small.

Immunogenicity Data – Protocol 004
Blood samples were taken from subjects in the CMI substudy and from subjects developing HZ for gpELISA, responder cell frequency (RCF) and INF-γ ELISPOT assays.

Antibody data from gpELISA assay appears to be a measure of postvaccination immune response. Considering the fact that the vaccine is acting as a "booster" in subjects with previous primary varicella infection, the kinetics of the antibody response might be expected to exhibit higher and more discriminatory titers at earlier time points, e.g., 2-3 weeks postvaccination.

Measures of cellular immunity, RCF and IFN-γ ELISPOT data, are limited by lower the relatively lower magnitude of response and relatively higher variability in assay results as well as the technical complexity of

handling the samples. The data derived from RCF and ELISPOT at this point do not appear to add significantly to the information derived from gpELISA data.

Naturally Occurring HZ – Protocol 004

Following naturally occurring HZ, both ZOSTAVAX™ and placebo recipients exhibited larger immune responses as measured by gp ELISA when compared to immune responses seen postvaccination with ZOSTAVAX™. 6 weeks following ZOSTAVAX™ vaccination, gpELISA geometric mean titer (GMT) was 575 (95% CIs: 442, 511) and geometric mean fold rise (GMFR) was 1.7 (95% CIs: 1.6, 1.8). In contrast, 6 weeks following onset of herpes zoster gpELISA GMT was 2042 (95% CIs: 1805, 2310) and GMFR was 3.2 (95% CI: 2.6, 3.9) in ZOSTAVAX™ recipients; and gpELISA GMT was 2260 (95% CI: 2070, 2467) and GMFR was 3.1 (95% CIs: 2.7, 3.5) in placebo recipients. The clinical relevance of this higher response with respect to risk and severity of subsequent HZ in naturally occurring HZ as compared to HZ occurring postvaccination with ZOSTAVAX™ remains to be elucidated.

Safety Data – Protocol 004

Overall, safety data from the pivotal clinical study demonstrate no particular pattern of postvaccination adverse events such as deaths, hospitalizations or serious adverse events.

In all cases in which VZV DNA was detected by PCR from suspected HZ lesions in Protocol 004, the strain identified was wild-type; the attenuated vaccine strain was not detected in any case. Protocol 001 did include one case of varicella-like rash with onset at Day 310 postvaccination which was positive for Oka/Merck varicella virus by PCR.

Reactogenicity following vaccination, as measured in the AE Monitoring Substudy, was higher in ZOSTAVAX™ recipients compared to placebo recipients for rate of injection-site adverse events (48% in of zoster vaccine recipients, 17% of the placebo recipients). This was primarily due to vaccine-associated increases in solicited adverse events, erythema, pain/tenderness and swelling. Several types of unsolicited injection-site reactions, including swelling, warmth and pruritus were reported at higher rates in ZOSTER™ recipients. There were no notable differences in the rates of systemic vaccine-associated AEs, including fever.

Local injection-site reactions were relatively higher in females (~5-10% in placebo recipients; ~40-50% in ZOSTAVAX™ recipients) versus males (~4-8% in placebo recipients; 15-25% in ZOSTAVAX™ recipients).

Local injection site reactions were also relatively higher in the younger 60-69 year old cohort (~5-10% in placebo recipients; ~30-43% in ZOSTAVAX™ recipients) versus ≥ 70 year old cohort (~4-7% in placebo recipients; 20-30% in ZOSTAVAX™ recipients).

Safety Follow-Up – Protocol 004

Day 0-42 postvaccination safety follow-up data was collected using the Automated Telephone Response System (ATRS). 55% of all study subjects responded to the ATRS around Day 42 and study investigators added information for an additional 11% subjects over a 4 year period postvaccination. There are 1240 additional reports for subjects already accounted for in this dataset – some of these additional reports are added several years after the initial entry.

No information on the reporting rates is available for monthly ATRS contacts used to identify potential cases of HZ in all subjects and to provide safety follow-up in the Adverse Event Monitoring Substudy (AE Substudy). Likewise, there is no information on reporting rates by month, by site, by baseline characteristics and by study outcomes.

Study termination procedures included directly querying each subject. The study reports final accounting (~2-5 years postvaccination) for 99% of subjects, consisting of those identified as directly contacted by study personal at the conclusion of study and those confirmed as deceased. Less than 0.5% of all study subjects were identified as drop-outs or those lost to follow-up. In 99% of those reported as having contact at study termination, there is no date given for last contact. The proportion of subject termination records resulting from direct subject

contact and the proportion of subject records, if any, resulting from "pre-populated" data, i.e., derived from other data sources, is unclear.

No information is available regarding the identity of subjects 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 subject characteristics or differential follow-up and access to healthcare information might impact on the reported safety and/or efficacy of ZOSTAVAX™.

Per the sponsor comment on page 309 of Protocol 004 Clinical Study Report: "Due to the passive and inconsistent nature of safety data collection in the Routine Safety Monitoring Cohort for adverse experiences occurring from Day 43 postvaccination through study end, caution should be exercised when interpreting these particular data."

Limitations of Protocol 004

Although age is a primary determinant in the frequency and severity of HZ-related disease, there are relatively fewer subjects at the upper age range of the study population. Additionally, the study sought to enroll relatively healthy, older subjects, excluding those with common co-morbidities (e.g., regular use of inhaled corticosteroids; subject survival not estimated to be at least 5 years; subject homebound or not ambulatory; subject with cognitive impairment or severe hearing loss) any of which might have resulted directly or indirectly in lower efficacy estimates and higher reported rates of adverse events than those seen in Protocol 004. Additionally, this relatively healthy study population may not provide an adequate opportunity to evaluate whether or not the vaccine had any impact on zoster-related hospitalizations and other severe complications of HZ.

Since most study participants who developed HZ were treated with antivirals, the rate of HZ complications may have been decreased.

Given the lack of information on the proportion of subjects responding at the monthly ATRS contact and at study termination, and the documented deficiencies in subject reporting to the Day 42 safety follow-up, it is difficult to draw conclusions as to the relative safety of ZOSTAVAX™ at this time.

Protocol 009

This study evaluated safety of ZOSTAVAX™, comparing a higher potency dose (207,000 pfu) to a lower potency dose (58,000 pfu). The lower potency is in the range of the highest potency evaluated in the pivotal study, Protocol 004.

Subjects 50 years and older, stratified into two groups: 50-59 years old and ≥ 60 years old were enrolled in Protocol 009. Note: Protocol 004, the pivotal study, enrolled two age strata: 60-69 years old and ≥ 70 years old.

The two study endpoints for ZOSTAVAX™ were based upon the historical adverse event rate for PNEUMOVAX23™ and the assumption that no vaccine-related serious adverse events would occur, respectively. The clinical relevance of these two endpoints is unclear.

Subjects receiving the higher dose experienced higher rates of solicited and non-solicited vaccine-related injection site reactions, although few were characterized as severe. There did not appear to be a higher rate of systemic vaccine-related AEs.

The younger cohort (50-59 years old) experienced relatively higher rates of injection-site reactions as compared to the older cohort (≥ 60 years old). The younger cohort also characterized more specified systemic adverse events, e.g., headache, as severe.

No specific pattern of SAEs was observed, although 4 SAEs were seen in the higher dose group and 1 SAE in the lower dose group.

2.0 Introduction and Background

2.1 Epidemiology of Herpes Zoster

Varicella-zoster virus (VZV) is an alphaherpes virus and a member of the *Varicellovirus* genus in the *Herpesviridae* family of viruses. Infection in humans occurs via the respiratory tract and conjunctiva. As with other herpes viruses, VZV has the capacity to persist in the body after a primary infection, in the case of VZV in the sensory nerve ganglia.

Disease manifestions may include a mild, prodromal phase (malaise, fever) prior to the appearance of the typical pruritic, vesicular rash which can be distributed in a localized or diffuse pattern. Complications of primary varicella infection can include bacterial superinfection of involved skin and underlying soft tissues, and pneumonia particularly in adults. Infections may be severe and include septicemia, toxic shock syndrome, necrotizing fasciitis, osteomyelitis, bacterial pneumonia and septic arthritis. Less common complications can involve the central nervous system, e.g., cerebellar ataxia, encephalitis; liver and hematopoietic systems. Disseminated intravascular coagulation can occur in rare cases. Hospitalization rates of ~3/1,000 cases and death rates of ~1/60,000 cases have been reported following varicella infection. Adults, immunocompromised individuals and infants of mothers experiencing varicella rash in the perinatal period are all at increased risk of complications from varicella infection. Intrauterine infections, particularly early in gestation, can rarely result in congenital varicella syndrome.

Herpes zoster is due to reactivation of latent varicella zoster virus, usually many years following a primary varicella virus infection (chickenpox) and manifests as a unilateral, vesicular rash in a dermatomal distribution and systemic symptoms are unusual. Zoster-associated pain, paresthesias and pruritis usually resolve within a few weeks, but in some cases severe, debilitating pain and paresthesia may persist for a year or more and symptomatic treatment may be only partially effective. Other serious complications involve ocular and visceral organ involvement. While transmission of the virus to other individuals has been documented, it occurs rarely. Reactivation is associated with aging and immunosuppression. Individuals with intrauterine exposure or varicella at an early age (< 18 months) are also at higher risk of VZV reactivation.

VARIVAX™ (Varicella Virus Vaccine Live) a live, attenuated strain of the virus was licensed in the U.S. in 1995 for vaccination against varicella in individuals 12 months of age and older.

From the time of licensure to 2003, rates of primary varicella have decreased by approximately 85% as reported by the CDC Varicella Active Surveillance Project (VASP) with nationwide vaccine rate of 85% among the population for whom it is recommended. VASP is also monitoring rates of HZ, as circulating wild-type varicella has been suggested as a source of external boosting (i.e., exposure to varicella disease in the community) that prevents reactivation of VZV and subsequent HZ and its manifestations. Data from the Massachusetts Behavioral Risk Factor Surveillance System shows age-standardized rates of overall herpes zoster occurrence increasing from 2.77/1,000 to 5.25/1,000 (90%) in the period 1999–2003. This trend in both crude and adjusted rates was highly significant ($p < 0.001$), specifically in the 25–44 year and 65+ year age groups (Yih, 2005).

2.2 Regulatory Background

ZOSTAVAX™ has been formulated using the same varicella virus bulk product contained in the Merck VARIVAX™ and ProQuad™ vaccines. The varicella component contained in these latter two vaccines is indicated for vaccination against varicella in individuals 12 months of age and older.

ZOSTAVAX™ has not been licensed in any country to date.

The proposed trade name, ZOSTAVAX™, will be used throughout this document to indicate the formulations of the Varicella Virus Vaccine Live (Oka/Merck) studied in Protocols 001, 002, 003, 004, 005, 007, and 009. Only Protocols 004 and 009 are described in this briefing document.

2.3 Basis for Licensure

There is no current preventive treatment for herpes zoster.

The development strategy followed by Merck & Co., Inc. to support licensure of ZOSTAVAX™ in older adults was based upon the following:

- Demonstration of safety of a single dose of ZOSTAVAX™ in healthy adults 60 years and older
- Demonstration of efficacy of a single dose of ZOSTAVAX™ in healthy adults 60 years and older [decreases in the incidence of HZ, the incidence of post-herpetic neuralgia (PHN), the burden-of-illness (BOI) score, the duration of PHN and interference with activities of daily living (ADLI).]
- Demonstration of clinical lot-to-lot consistency by comparison of major efficacy endpoints (incidence of HZ, incidence of PHN and changes in BOI scores) in healthy adults aged 60 years and older by ZOSTAVAX™ lot administered
- Demonstration of safety (42 days postvaccination) of a higher potency ZOSTAVAX™ in adults aged 50-59 years.

3.0 OVERVIEW OF ZOSTER VACCINE CLINICAL STUDIES

The Biologics License Application (BLA) contains safety, immunogenicity and efficacy data from Protocol 004, and safety data with or without immunogenicity data from six supportive clinical studies in adults: Protocols 001, 002, 003, 005, 007 and 009. Reports from Protocol 012 and 049, used to support licensure of ProQuad™ and VARIVAX™, respectively are submitted. For each of these studies full study reports were submitted.

The overall safety database comprised approximately 21,000 subjects who received ZOSTAVAX™. 19,270 subjects received ZOSTAVAX™ in Protocol 004 and 698 subjects received ZOSTAVAX™ in Protocol 009.

Table 3.1 Overview of ZOSTAVAX™ Clinical Studies

Protocol #	001	002	003	004	005	007	009
Number of subjects	276	Dose 1: 398 Dose 2: 206	21	38,546	196	210	698
Number of ZOSTAVAX recipients	241	398	18	19,270	196	210	698
Population	Healthy adults Seropositive	Adults Healthy, DM or COPD Hx of varicella	Healthy adults Central & S. America & Philippines Low (≤5 gpELISA units/mL) or undetectable varicella-zoster virus antibody titer	Healthy Adults ≥ 60 yrs. old	Healthy adults Previous 1-2 doses zoster vaccine History of varicella	Healthy adults ≥ 60 yrs.	Healthy adults ≥ 50 yrs.
Strata Demographics	60-75 yrs: N = 144 ≥ 76 yrs: N = 132	60-75 yrs: ≥ 76 yrs	≥ 30 yrs: N = 21	60-69 yrs: ≥ 70 yrs:	61-89 yrs	None	50-59 yrs: ≥ 60 yrs:
# Doses	1	2	1	1	1	2	1
Schedule	0	0 & 18 mos.	0	0	0	0 & 42 days	0
Dose levels (pfu/dose)	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
Postvaccination Follow up	42 day safety, immunogenicity	42 day safety, immunogenicity	42 day safety, immunogenicity	42 day safety HZ ~2-4.5 yrs Immune ≤3 yrs.	42 day safety; 42 day-2 year immunogenicity	42 day safety, immunogenicity	42 day safety

(Source: BLA STN 125123, Clinical Study Reports & Synopses)

4.0 PIVOTAL SAFETY AND IMMUNOGENICITY STUDY - PROTOCOL 004

Title: Trial of Varicella-Zoster Vaccine for the Prevention of Herpes Zoster and its Complications Department of Veterans Affairs Cooperative Study #403

4.1 Objectives

Co-Primary Objectives

- To determine if immunization with zoster vaccine will reduce the incidence and/or severity of herpes zoster (HZ) and its complications, primarily post herpetic neuralgia (PHN), in persons 60 years of age and older.
- To determine if immunization with zoster vaccine will protect against PHN.

Secondary Objectives (originally designated as tertiary objectives)

- To determine if immunization with zoster vaccine will reduce the incidence of HZ.
- To determine if immunization with zoster vaccine will reduce the duration of HZ pain.
- To determine if immunization with zoster vaccine will reduce the Activities of Daily Living Interference (ADLI) in subjects who develop HZ.

Tertiary Objectives

- To assess the effect of the vaccine on the incidence of PHN using alternative definitions of pain that persists or appears more than 30, 60, 120, and 182 days after rash onset.
- To examine the vaccine efficacy and immunogenicity of three consistency lots of the vaccine.
- To examine the effect of a reduction in the plaque forming unit (PFU) content of the vaccine over time on its efficacy.
- To assess the varicella zoster virus (VZV) - specific immune response to the zoster vaccine.
- To collect specific data on the impact of HZ and its complications on the quality of life of older persons.
- To provide specific data on the natural history of HZ in older persons, during a time when most will be treated acutely with an antiviral drug (acyclovir, famciclovir, or valacyclovir).
- To assess the safety profile of the zoster vaccine in persons 60 years of age or older.
- To explore potential covariate effects of gender, age, antiviral and analgesic medications on the burden-of-illness (BOI) and vaccine efficacy in study subjects who develop HZ.
- To describe the HZ-related health care resource utilization (beyond study protocol mandated visits) and out-of- pocket expenses incurred by study subjects with HZ.
- To determine whether use of the zoster vaccine is associated with a significant reduction in the number of nonprotocol-mandated HZ-related health care contacts relative to placebo recipients.

4.2 Design

Protocol 004 is described as a randomized, double-blind, placebo-controlled, 22-center study of the safety, efficacy, immunogenicity and consistency of three manufacturing lots of ZOSTAVAX™ in relatively healthy adults (≥ 60 years of age).

4.3 Population

The study planned enrollment of approximately 37,200 adults 60 years of age and older, including a target enrollment of approximately 11,160 subjects in the 60 to 69 years of age stratum and approximately 7440 in the ≥ 70 years of age stratum in each vaccination group.

4.4 Enrollment Criteria

Inclusion Criteria

- History of varicella or long-term (≥30 years) residence in the continental USA.
- 60 years of age or older.
- Informed consent obtained from the subject.

Exclusion Criteria

- Immunosuppression resulting from disease (e.g., malignancy; human immunodeficiency virus [HIV] infection), corticosteroids (except intermittent topical or inhaled corticosteroid [<800 mcg/day beclomethasone dipropionate or equivalent]), or other immunosuppressive/cytotoxic therapy (cancer chemotherapy or organ transplantation).
- Active neoplastic disease (except local skin cancer or other malignancies [e.g., prostate cancer] that was stable in the absence of immunosuppressive/cytotoxic therapy).
- Prior HZ.
- Prior receipt of varicella vaccine.
- Allergic sensitivity to neomycin.
- History of anaphylactoid reaction to gelatin.
- Significant underlying illness that would be expected to prevent completion of the study (e.g., life-threatening disease likely to limit survival to less than 5 years).
- Not ambulatory (bed-ridden or homebound).
- Receipt of immune globulin or any other blood product within 3 months before or planned during the 3- to 5-year study period.
- Receipt of any other vaccines within 1 month before study vaccination (2 weeks in the case of inactivated influenza vaccines or other inactivated vaccines [e.g., diphtheria toxoid, tetanus toxoid, pneumoccocal vaccine, hepatitis A vaccine, hepatitis B vaccine]), or scheduled within 6 weeks after study vaccination.
- Receipt of antiviral therapy at the time of enrollment, in order to avoid potential confounding of vaccine effectiveness.
- Any other condition (e.g., extensive psoriasis, chronic pain syndrome, cognitive impairment, severe hearing loss) that, in the opinion of the site investigator, might have interfered with the evaluations required by the study.
- Intercurrent illness (e.g., urinary tract infection, influenza) that might have interfered with the interpretation of the study results.
- Female and premenopausal (women who entered the study had to be postmenopausal).
- Unlikely to adhere to protocol follow-up.
- Involved in a conflicting (vaccine or investigational drug) clinical trial.
- History of recurrent herpes simplex virus (HSV) and had more than 3 episodes per year for which the subject was treated with episodic antiviral therapy (e.g., 400 mg oral acyclovir 3 times daily for 5 days) or was on constant daily antiviral therapy.
- History of multiple sclerosis, in order to avoid potential confounding of vaccine effectiveness due to antiviral or immunosuppressive therapy.

4.5 Vaccine Administration

4.5.1 General Vaccine Information

All investigational vaccine was supplied lyophilized in 0.7-ml, single-dose vials. Vaccine was stored at ≤ -20ºC at Merck and at -15ºC during distribution and storage at the study sites. Sterile diluent (water without preservatives) was supplied in 0.7-ml vials. It could be stored refrigerated at 2-8ºC or at room temperature. The drug product is reconstituted with sterile diluent just prior to use.

The placebo contained the same stabilizers as the investigational vaccine, but did not contain the Oka/Merck varicella virus or neomycin. The placebo was visibly distinct from the investigational vaccine.

A single 0.5 mL dose was administered subcutaneously into the deltoid area of the non-dominant arm.

4.5.2 Protocol Specific Vaccine Information

Pivotal study, Protocol 004, employed 12 clinical lots of ZOSTAVAX™ administered in a volume of 0.5mL. 3 clinical lots were stored frozen until reconstitution and administration as described above, while an additional 3 clinical lots were derived from these lots and subjected to accelerated aging by storage at 2-8ºC for 3 months to intentionally decrease the potency as measured by plaque-forming units. The remaining 6 clinical lots were derived from additional "parental" lots (2 accelerated aged lots from each of 3 parental lots) and subjected to storage at 2-8ºC for 3 months to intentionally decrease the potency as measured in plaque-forming units.

4.5.3 Dose Selection

Most of the ZOSTAVAX™ clinical lots were "aged" by storage at higher than recommended temperature (2-8ºC) to evaluate the safety and efficacy at the anticipated expiry, approximately 20,000 plaque-forming units (pfu)/0.5 mL dose.

Table 4-1 ZOSTAVAX™ Lots Used in Protocol 004

"Parental" Lot*	Clinical Lot Number	Initial (Release) Potency PFU/0.5 mL Dose	Aged
Not applicable	1535W-E046	48,911	Not aged
Not applicable	1536W-E047	57,092	Not aged
Not applicable	1537W-E048	46,291	Not aged
A	1553W-E462	33,000	Aged
B	1554W-E463	39,600	Aged
C	1555W-E464	32,700	Aged
D	1562W-E471	27,300	Aged
E	1563W-E472	27,150	Aged
F	1564W-E473	33,500	Aged
D	1588W-G479	22,000	Aged
E	1589W-G480	26,850	Aged
F	1590W-G481	25,500	Aged
*For ease of review this table arbitrarily assigns parental lots a unique identifier.			

(Source BLA 125123, Protocol 004 Table 5-1)

4.6 Other Products Used in Protocol 004

Antiviral Therapy

Famciclovir (Smith Kline Beecham Pharmaceuticals, UK, or Novartis Pharmaceuticals, USA) 500mg every 8 hours for 7 days

Subjects evaluated within 72 hours of onset of rash due to suspected herpes zoster were offered famciclovir. If subject were first seen beyond 72 hours after rash onset, famciclovir could be offered at the physician's discretion.

Analgesia

Pain was managed at the discretion of the study site investigator and could include acetaminophen, non-steroidal anti-inflammatories, opiates, and topical anesthetics.

5.0 ENDPOINTS

5.1 Primary and Secondary Endpoints

Table 5-1 Summary of Primary and Secondary Endpoint Results and Analyses

		Endpoint/Analysis	Success Criteria
Co-Primary	1	Herpes Zoster Burden of Illness (HZ BOI) subjects ≥ 60 years of age VE_{BOI} = HZ $BOI_{PLACEBO}$ - HZ $BOI_{VACCINE}$	Point estimate > 47% LL 95% CI > 25%
	2	Incidence of Post-herpetic neuralgia (PHN) subjects ≥60 years of age $VE_{PHN} = PHN_{PLACEBO} - PHN_{VACCINE} / PHN_{PLACEBO}$	Point estimate > 62% LL 95% CI > 25%
Secondary*	1	Incidence of HZ in subjects ≥60 years of age $VE_{HZ} = HZ_{PLACEBO} - HZ_{VACCINE} / HZ_{PLACEBO}$	LL 95% CI > 25%
	2	Duration of clinically significant pain vaccine and placebo, in subjects ≥60 years of age Log-rank test	p-Value < 0.001
	3	Substantial Interference with Activities of Daily Living (SADLI)[4] Above and Beyond VE_{HZ} subjects ≥60 years of age SADLI = 1– Relative Risk SADLI / Relative Risk HZ	p-Value LL 95% CI > 0
LL = lower limit * Originally designated as tertiary endpoints, but during the study designated secondary endpoints.			

(Source: STN 125123 Protocol 004 Section 7.1.2.2)

5.1.1 Co-primary Endpoints Defined

- Herpes Zoster Burden of Illness Score (HZ BOI)
  A composite endpoint measuring incidence, severity and duration of pain:

  Proportion of all subjects within treatment group who developed HZ
  X
  Mean severity-by-duration score of subjects who developed HZ
  (weekly worst pain score multiplied by 7 days; scored on a 0-10 scale, 10 = worst pain)

  Note: All pain scores reported for Days 0-30 after onset of HZ rash were included, but only pain scores ≥ 3 were included after Day 30 following onset of HZ rash.

- Incidence of Postherpetic Neuralgia (PHN) in each treatment group
  HZ-associated pain scored ≥ 3 persisting or appearing at least 90 days after onset of HA rash. (Scored on 0-10 scale, 10 = worst pain). The cutoff for the time defining PHN was revised during the study from 30 days to 90 days.

5.1.2 Secondary Endpoints Defined

NOTE: During the course of the study these endpoints were "elevated" from tertiary to secondary endpoints

- Incidence of Herpes Zoster (HZ)
  Number of evaluable HZ cases per 1000 person-years of follow-up per treatment group

- Duration of Clinically Significant HZ Pain
  Number of days between the first day after rash onset when the subject had a "worst pain" score of ≥ 3 (as reported on either IZIG or ZBPI) and the first visit when the "worst pain" score reported on

ZBPI was reported as <3 and remained <3 for the remainder of the follow-up period (up to 6 months after HZ rash onset) per treatment group.

- 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 per treatment group.

  Average of scores for seven pain interference items used a 0-10 scale, with 0 being no interference and 10 being maximum interference:
    - General activity
    - Mood
    - Walking ability
    - Normal work
    - Relations with others
    - Sleep
    - Enjoyment of life

5.1.3 Selected Tertiary Endpoints

- PHN Using Alternative Definitions
  Pain that persists or appears more than 30, 60, 120 and 182 days after rash onset

- Efficacy and Immunogenicity of 3 Consistency Lots of the Vaccine

- Effect of a Reduction in Plaque-Forming Unit (pfu) Content Over Time on Vaccine Efficacy

- VZV-Specific Immune Responses
  At baseline, Week 6, and Months 12, 24 and 26 post-vaccination

- Impact of HZ and Its Complications on Quality of Life of Older Persons

- Natural History of HZ in Older Persons
  Most subjects were treated with an antiviral drug (acyclovir, famciclovir or valacyclovir)

- Safety Profile of Zoster Vaccine in Persons ≥ 60 Years Old

- Evaluation of Potential Covariates

- Age, gender, and antiviral and analgesic medication usage

6.0 LABORATORY METHODS, SURVEILLANCE AND MONITORED PARAMETERS

6.1 Laboratory Methods

Evaluation of Suspected HZ
Lesion specimens collected from all suspected HZ cases at 1 of 2 central laboratories were forwarded to Central Laboratory PCR for VZV & HSV. PCR testing utilized PCR primers to distinguish between HSV and VZV infections. Culture of VZV was performed when local laboratory facilities were available, thus, culture was not attempted at all study sites.

Blood Samples
Cell Mediated Immunity (CMI) Substudy: The ZOSTAVAX™/VZV immune response was evaluated in approximately 1200 subjects (~600 each from the San Diego and Denver study sites; ~ 600 subjects

between 60 and 69 years old and ~ 600 subjects ≥ 70 years old). Enrollment and blood sampling began approximately 1 year after initiation of Protocol 004. Whole blood samples for VZV IFN-γ ELISPOT and RCF assays and serum samples for VZV-specific gpELISA antibody assays were collected just prior to vaccination, and at Week 6 and at months 12 ,24 and 36 postvaccination.

Naturally occurring HZ: Blood samples were obtained at Day 1, week 3 and week 6 following HZ rash onset.

Assay Methods

VZV PCR

DNA was extracted from specimen using ---------- PCR utilizing virus-specific primers and fluorescent probes to detect and discriminate among: Wild-type/Oka-parent VZV (VZV-WT/VZV-P); Oka-type attenuated VZV (VAV-O), the vaccine strain; and HSV DNA (HSV types 1 and 2).

VZV Responder Cell Frequency (RCF)

Lymphocyte proliferation was measured by limiting dilution assay after a 10-day incubation of PBMC + VZV antigen, followed by 3H-thymidine pulse (6 hrs.). Counts per minute (CPM) / well determined with positive well indicated ≥ 1 responding cell. Results were calculated as number of VZV-specific responder cells /100,000 PBMCs.

VZV IFN-γ ELISPOT

PBMCs were stimulated by exposure to VZV antigen (prepared from a stock of UV-inactivated Oka/Merck vaccine virus). A mouse monoclonal antibody was used to coat the culture plates and bind IFN-γ produced upon incubation of PBMCs with VZV antigen. After PBMCs were washed away a second biotinylated monoclonal antibody was used to bind IFN-γ remaining on the plate (bound to the first antibody). Alkaline phosphatase-streptavidin binds the biotinylated antibody and reacts with a chromogenic substrate (NBT/BCIP) and the resulting dark blue spots are then counted as a measure of the number of cells that produced IFN-γ in response to VZV antigen. Results reported as frequency of spot forming cells (SFCs) / 10^6 PBMCs. If results were negative, zero or <2, result reported as <0.5.

gpELISA

This method detects antibodies to VZV glycoprotein (gp), which have been purified from MRC-5 cells infected with the KMcC strain of VZV by lectin affinity chromatography. Serum sample titers as determined by gpELISA are shown to correlate with neutralizing antibody titers.

VZV glycoprotein (gp) antigen from VZV-infected MRC-5 cells or from uninfected MRC-5 cells (Tissue Culture Controls or TCC) was adsorbed to polystyrene microtiter wells and used as the solid phase antigen. Experimental, control, and standard curve sera were incubated in the VZV gp-coated and TCC-coated wells (2 wells for each antigen). For each serum sample, a delta optical density (DOD) is calculated as the difference between the average optical density (OD) of the 2 VZV antigen wells and the average OD of the 2 TCC wells. Quantitation was obtained by comparison of sample DOD with a standard curve. Results for the assay were reported as concentration of antibody in gpELISA units/mL.

The negative control used for this assay was an individual human serum at a dilution of 1:50, found to be negative for anti-VZV. The high-positive control was a VZV antibody-positive serum, diluted 1:500, which gave a response in the assay at the upper end of the standard curve. The low positive control was a VZV antibody-positive serum diluted 1:50, which gave a response in the assay at the lower end of the standard curve. A VZV antibody-positive individual human serum was used to generate a standard curve.

6.2 Safety Surveillance and Monitoring

- **Automated Telephone Reporting System (ATRS)**

At approximately 42 days postvaccination, all subjects were instructed to call a toll-free ATRS number to report safety-related information. Subjects were asked a serious of programmed questions regarding occurrences of rash, unusual reactions, hospitalizations, disability, life-threatening events, new diagnosis of cancer, overdose of any medication.

Subjects were also instructed to call the ATRS on a designated day each month to answer a series of pre-programmed questions to ascertain whether or not the subject had, at that time or during the previous 30 days, signs and/or symptoms compatible with HZ.

If a subject failed to call the ATRS when scheduled, the ATRS initiated 4 telephone calls to the subject over 96 hours. If these telephone calls failed to establish contact, the ATRS faxed a notification of failed contact to the local Study Coordinator.

If any response was suggestive of HZ, the subject was instructed by the ATRS to immediately telephone his/her local Study Coordinator to be evaluated. Also, ATRS faxed a copy of the subject's responses to the local Study Coordinator, notifying the coordinator to immediately establish contact with the subject.

A voice message center allowed subjects to leave detailed messages for local Study Coordinator.

- **Adverse Event Monitoring Substudy / Vaccine Report Cards (VRCs)**

The Adverse Event (AE) Monitoring Substudy planned enrollment of ~6000 subjects, to include ~300 subjects from each of the participating study sites. Once each site had established routine enrollment into the main study, subjects were to be consecutively enrolled into the AE Monitoring Substudy at the time they were enrolled. Vaccine Report Cards (VRCs) specifically queried for specific solicited adverse events (AEs) as follows:

Days 0-4 postvaccination: Swelling, redness, pain, tenderness
Days 0-21 postvaccination: Temperature
Days 22-42 postvaccination: Temperature if felt by subject to be abnormal; unsolicited AEs
Days 0-42 postvaccination: Rash looking like chicken pox or shingles, other complaints or illnesses

Site personnel reviewed available medical records to identify any additional AEs occurring Days 0-42. Hospitalizations occurring after the 42-day postvaccination period were tracked using monthly subject reporting to the Automated Telephone Response System.

Subjects enrolled in the AE Monitoring Substudy were excluded from enrollment in the CMI Substudy.

- **Routine Safety Monitoring Cohort**

The cohort includes all subjects not enrolled in the Adverse Event Monitoring Substudy. Days 0-42 subjects were monitored as described in the ATRS monitoring section and after Day 42 safety follow-up data was passively collected. Site personnel were expected to review available subjects' medical records to capture data relevant to adverse experiences or potential case of HZ.

- **Serious Adverse Events (SAEs) and Deaths**

Follow-up of a reported SAE was the same for the AE Monitoring Substudy and the Routine Safety Monitoring Cohort. Narratives are provided for SAEs occurring on study.

Narratives of serious adverse experiences with onset dates between Days 0 and 42 postvaccination that led to death are submitted in the study report.

Narratives are not provided for all deaths reported in the entire study period. Only the incidence of death was monitored throughout the entire study and used to compare the mortality rates between the 2 vaccination groups.

- **Evaluation of Suspected Herpes Zoster**

According to the protocol serial evaluation of by study personnel were to begin within 24 hours of first reported symptoms or as soon as possible thereafter and continuing over ≥ 182 days according to a protocol-specific schedule. Pain was evaluated using worst pain score (0-10 point scale, 10 = worst pain) on (time since rash onset) Days 1-3; 4 or 5; 6, 7, or 8; 9, 10 or 11; weekly on Weeks 2-8 and afterwards through Day 182 or until worst pain score has been below 3 for at least two consecutive weeks.

All pain scores reported for Days 0-30 were included, but only pain scores ≥3 were included after Day 30 in the calculation of BOI scores.

Pain scores of ≥ 3 are assumed to correlate with interference in activities of daily living.

Pain scores were recorded after first onset of rash and prior to the first visit using the **Initial Zoster Impact Questionnaire (IZIQ)** and at subsequent timepoints using the **Zoster Brief Pain Inventory (ZBPI)**. The Brief Pain Inventory was originally designed to measure cancer pain (Cleeland 1994) and its evaluation of "worst pain in the last 24 hours" is reported to be a valid and responsive measure of HZ-related pain, correlating with changes in responses to health status questions as reported in results from a validation study conducted in 121 HZ subjects aged 60 years and older enrolled within 14 days of rash onset (Coplan 2004).

- **Clinical Evaluation Committee (CEC)**

The 5-member Clinical Evaluation Committee (CEC), blinded to treatment, clinical and laboratory information, evaluated all suspected HZ cases according to a Standard Operating Procedure (SOP). Blinded information including digital photos of rashes were evaluated individually by each CEC member. These results were used in determining evaluable cases of HZ when PCR or culture confirmation were not available. In addition, a comparison was made between those cases determined by clinical laboratory testing (PCR or culture) and the corresponding determination for the same cases made by CEC.

A hierarchical determination of HZ considered the results of PCR first, culture results next for those without PCR determination and CEC determination for those without either PCR or culture determination for each suspected HZ case. Suspected rashes determined not to be caused by HZ or considered indeterminable were classified as "non-evaluable." Non-unanimous cases were reviewed at subsequent CEC meetings. Cases that remained "Indeterminate" after a second CEC meeting were classified as "Not a clinically diagnosed case of HZ"

- **Data Safety Monitoring Board (DSMB)**

A DSMB was responsible for reviewing the progress of the study, monitoring subject intake, outcomes, possible adverse experiences after vaccination, and various ethical issues and making recommendations as to whether the study should continue or terminate.

DSMB Interim Monitoring

Interim reports were provided to the DSMB by a designated unblinded biostatistician at the Veterans Affairs Cooperative Studies Program Coordination Center, who was not otherwise associated with this program.

Approximately two weeks prior to each of their meetings, the DSMB members were to receive an interim monitoring report including all analyses previously requested. Any unblinded tables that have been prepared by the third-party unblinded biostatistician used "X" or "Y" for treatment group labels. The actual identity of treatments was not revealed to the DSMB unless requested by the DSMB. No individuals other than the third-party unblinded biostatistician and the DSMB were allowed to see or know the content of the unblinded tables.

Interim Safety Monitoring:
The DSMB reviewed adverse experience data periodically and in the event that severe adverse reactions or increased incidence of HZ are noted to be excessive in the vaccine arm relative to the placebo arm, the DSMB may consider stopping recruitment into the study.

7.0 CASE DEFINITIONS

7.1 Suspected Herpes Zoster

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.

7.2 Evaluable Herpes Zoster (confirmed case)

Diagnosis of HZ was based upon a hierarchical approach: suspected cases were to be confirmed as VZV positive or negative by PCR whenever possible; suspected cases that could not be confirmed as positive or negative by PCR could be identified by a positive VZV viral culture; and lastly, cases that could not be confirmed as positive or negative by PCR or positive by viral culture were to be determined by a Clinical Evaluation Committee (CEC) which evaluated all suspected cases even those confirmed by PCR testing or viral culture. (CEC HZ determinations and hierarchical testing determinations of HZ cases were later compared in the efficacy analyses.)

7.3 Post-herpetic Neuralgia (PHN)

Using a pain scale of 0-10 with 0 = no pain & 10 = worst pain, PHN was defined as pain score ≥ 3 persisting or appearing more than 90 days after HZ rash onset (revised during the study from originally definition using a 30-day cutoff).

8.0 STATISTICAL CONSIDERATIONS

Loss to follow-up
Loss-to-follow-up was considered to have little impact on the planned power of the efficacy analyses. If a subject was lost to active follow-up during the trial but later contacted and no case of HZ had been missed, no information was considered lost with regard to the efficacy analyses.

All randomized subjects who were lost to follow-up before developing HZ during the study contributed follow-up information to the efficacy analyses until the date of the last completed contact. The analyses treated these subjects similar to those subjects who remained in contact with the study site throughout the study and did not develop HZ before the trial was terminated.

Although protocol-specified, the date of last contact is blank in the termination datasets for 99% of subjects not identified as deceased, lost to follow-up or dropouts.

8.1 Randomization and Stratification

Subjects were randomized in a 1:1 ratio to receive vacccine or placebo. Eligible subjects were sequentially assigned an allocation number (AN) in numerical order from the allocation schedules provided by the Cooperative Studies Program Coordination Center.

Randomization was stratified by site and by age group: 60-69 years and ≥ 70 years. Two (2) separate allocation schedules were generated; one for individuals 60 to 69 years of age and one for individuals $\geq$ 70 years of age. Randomization numbers were assigned sequentially within each age stratum at each

participating site as subjects were enrolled. Target enrollment in each treatment group (vaccine or placebo) was ~11,160 in the 60-69 year age stratum and ~7440 in the ≥70 year age stratum.

8.2 Blinding

Placebo and vaccine were visually distinct. Therefore, an independent third party (vaccine technician) was responsible for labeling syringes and reconstituting and administering the vaccine/placebo. This unblinded person had no subsequent role in the assessment of subjects and did not maintain any separate record of study vaccine or placebo assignments. Subjects, site investigators and site personnel, and Veterans Affairs Cooperative Studies Program Coordination Center (CSPCC), Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) and Merck & Co., Inc. personnel, were all blinded.

8.3 Unblinding

A preliminary analysis of data from the CMI Substudy obtained at Day 0 and Day 42 postvaccination was performed. No clinical efficacy data were included in this preliminary analysis, which was performed by an independent, unblinded Veterans Affairs Cooperative Studies Program (CSP) Biostatistician who was not involved in the day-to-day operation of the study. The results were summarized by group and no individual identification of the subjects was disclosed. These results were made available to the management of the Clinical, Biostatistics, Regulatory, and Manufacturing departments at Merck & Co., Inc., and the Director of the West Haven Veterans Affairs Cooperative Studies Program Coordination Center (VA CSPCC). The DSMB was also provided with a copy of the preliminary analysis report. The conduct of the study was unaffected by this analysis.

8.4 Sample Size

The study used a conservative estimate of HZ incidence of 3 / 1000 person-years in individuals aged ≥ 60 years, and estimated 10% of subjects lost to follow-up annually, a total enrollment of 37,500 subjects randomized 1:1 to vaccine or placebo with approximately 4.5 years of follow-up per subject was planned. Fewer subjects aged ≥ 70 years were planned to be enrolled, as the incidence rates of HZ and PHN are relatively higher in this older age group.

8.5 Interim Analyses

Two interim analyses of efficacy endpoints were planned but later cancelled. No formal interim analyses were performed, however sample size re-estimation and other analyses were conducted.

8.6 Population for Analyses

The primary efficacy analysis population included all subjects ≥ 60 years old. This modified intent-to-treat (MITT) population excluded subjects with less than 30 days of follow up and those who developed HZ in the first 30 days following vaccination.

9.0 RESULTS

Study period:	06-Nov-1998 to 30-Apr-2004
Last HZ case accrued:	30-Sep-2003
Last subject terminated:	28-Apr-2004 (except one subject with termination date 20-Sep-2004)

9.1 Population Enrolled / Disposition

Age distribution in the treatment groups for MITT population, and CMI and AE Monitoring Substudies were all similar to that in the overall study population.

While a higher proportion of males (59%) was enrolled the study overall, a lower proportion of males were enrolled in the CMI and AE Monitoring Substudies (55.5% and 55.6% respectively).

Although the proportion of males in the CMI Substudy was 55.5%, a lower proportion was randomized to the zoster vaccine group within the CMI Substudy (50.4%).

Racial characteristics of the study populations were largely similar except that a lower proportion of Black subjects were enrolled in the CMI Substudy compared to the overall study (0.5% vs. 2.1%). The fact that 95% of all study participants were White makes it difficult to draw conclusions as to any differences in safety or efficacy based upon race.

The baseline characteristics of marital status, education, work status, health status by EuroQol, and functional/activity measures were similar in the AE Monitoring Substudy and the overall study population.

All baseline characteristics in the zoster vaccine and in the placebo groups were similar within each of the study subpopulations (MITT, CMI Substudy and AE Monitoring Substudy populations).

Table 9-1 Subject Disposition

Protocol 004	Zoster Vaccine (N=19270)		Placebo (N=19276)		Total (N=38546)	
	n	(%)	n	(%)	n	(%)
Vaccinated	19270	(100)	19276	(100)	38546	(100)
Completed	18359	(95.3)	18357	(95.2)	36716	(95.3)
Discontinued	911	(4.7)	919	(4.8)	1830	(4.7)
Reasons for discontinuations:						
Died	793	(4.1)	792	(4.1)	1585	(4.1)
Withdrawn from the study	57	(0.3)	75	(0.4)	132	(0.3)
Lost to follow-up	53	(0.3)	40	(0.2)	93	(0.2)
Other†	8	(0.0)	12	(0.1)	20	(0.1)
Reasons for withdrawal or lost to follow-up:						
All	118	(0.6)	127	(0.7)	245	(0.6)
Changed mind about being in study	31	(0.2)	40	(0.2)	71	(0.2)
Moved away	13	(0.1)	10	(0.1)	23	(0.1)
Discontinued due to adverse experience	11	(0.1)	18	(0.1)	29	(0.1)
Other‡	62	(0.3)	59	(0.3)	121	(0.3)
Missing	1	(0.0)	0	(0.0)	1	(0.0)

† Reported "Other" as reason for study termination in Case Report Form.
‡ Reported "Other" as reason for withdrawal, or "Lost to follow-up" in Case Report Form.
Completed = Completed end-of-study interview N = # subjects randomized n = # subjects in respective category.

(Source: STN 125123; Protocol 004, Tables 6-1, 6-2, 6-3)

Subject disposition in CMI Substudy and AE Monitoring Substudy were similar to that in Protocol 004.

9.2 Study Follow-Up

Herpes Zoster Case Follow-up

Subjects in the MITT population were followed for an average of 3.09 years (median: 3.10 years; range: 31 days to 4.90 years) postvaccination for the development of suspect HZ. According to the protocol, each suspected case of HZ was to be followed for HZ pain for 6 months after rash onset. Table 9-4 summarizes the length of follow-up for evaluable HZ pain by vaccination group. As shown in this table, more than 96% of evaluable HZ cases had follow-up (at least for 175 days). Among those subjects followed for less than 175 days, the majority reported a worst pain score ≤1 and rash healed at their last visit.

Table 9-2 Follow-Up of Evaluable HZ Pain After Rash Onset in MITT Population

	Placebo	Zoster	Total
# Evaluable HZ cases	642	315	957
Followed ≥ 182 days	586 (91.3 %)	287 (91.1%)	873
Followed ≥175, <182 days	38 (5.9%)	13 (4.1%)	51
Followed < 175 days	18 (2.8%)	15 (4.8%)	33
No Pain follow up	13 (2.0%)	8 (2.5%)	21

(Source: (STN 125123; Protocol 004 Table 11-10)

Clinical lots were introduced into the study in a dose de-escalation fashion, and equal numbers of subjects received each of the three clinical lots within each group. The administered dose and time of follow-up were both a function of the date the subject enrolled in the study. All immunogenicity data were obtained from Groups 3 and 4.

Table 9-3 Follow-Up by Vaccine Potency (ZOSTAVAX™ recipients)

	Group 1	Group 2	Group 3	Group 4
Vaccine recipients (N)	835	978	8720	8737
Dose (pfu / 0.5ml dose)	50,000-62,000	34,000-42,000	26,000-33,000	21,000-26,000
Dates administered	11/98 - 11/99	04/99 – 11/99	07/99 – 12/00	07/00 – 09/01
Approx. Avg. F/U (days)	1400	1400	1200	900
*Clinical Lot denoted by last 3 digits of Clinical Lot number. See Table 4-1 for further information on Clinical Lots. #Accelerated aged lot groups				

(Source: STN 125123, Protocol 004 DEMO datasets)

9.3 Determination of HZ Cases

The following table provides information on the proportion of HZ cases confirmed by method of ascertainment. Of suspected cases of HZ, 88.4% tested positive by PCR. Of suspected cases determined evaluable cases of HZ, 93.4% tested positive by PCR. In all cases in which VZV DNA was detected by PCR, the strain identified was wild-type, i.e., no Merck/Oka vaccine strain-induced HZ was found in this study.

Table 9-4 Determination of Evaluable HZ Cases*

Criteria			Zoster Vaccine (N = 19270) (M = 467)		Placebo (N = 19276) (M = 799)	
PCR	Virus Culture	Clinical Adjudication	Evaluable n (%)	Non-Evaluable n (%)	Evaluable n (%)	Non-Evaluable n (%)
All suspected HZ cases occurring ≥ 30 days postvaccination (MITT definition)						
Total			316 (67.7)	151 (32.3)	644 (80.6)	155 (19.4)
VZV-positive†	Not considered	Not considered	295 (63.2)	0 (0.0)	602 (75.3)	0 (0.0)
VZV-negative†	Not considered	Not considered	0 (0.0)	88 (18.8)	0 (0.0)	91 (11.4)
HSV-positive‡	Not considered	Not considered	0 (0.0)	23 (4.9)	0 (0.0)	21 (2.6)
VZV-positive And HSV-positive	Not considered	HZ case by CEC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Non-HZ case by CEC	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Inadequate or missing specimen	Positive for VZV	Not considered	2 (0.4)	0 (0.0)	8 (1.0)	0 (0.0)
	Positive for HSV	Not considered	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.3)
	No virus isolated or no viral culture	HZ case by CEC (seen early)	19 (4.1)	0 (0.0)	34 (4.3)	0 (0.0)
	No virus isolated or no viral culture	HZ case by CEC (seen late)	0 (0.0)	3 (0.6)	0 (0.0)	4 (0.5)
	No virus isolated or no viral culture	Non-HZ case by CEC	0 (0.0)	36 (7.7)	0 (0.0)	36 (4.5)

*Including multiple cases/subject
†Samples were determined as HSV-negative or inadequate for HSV testing
‡These samples were determined as VZV-negative.
Percentages calculated based on total number of suspected HZ cases per group (i.e., 100 x n/M)
Seen early: Suspected HZ seen during the rash stage (crusted vesicles or earlier).
Seen late: Suspected HZ first seen beyond crusting stage of rash.
Evaluable: Suspected HZ, 1. Confirmed as VZV-positive by PCR or culture (if PCR result unavailable)
2. Adjudicated as HZ by CEC if not confirmed by laboratory results.
N = Number of subjects randomized.

M = Number of suspected HZ cases.
n = Number of cases in the respective category.
PCR = Polymerase chain reaction.
HZ = Herpes zoster.
CEC = Clinical Evaluation Committee.
VZV = Varicella-zoster virus.
HSV = Herpes simplex virus.
2 placebo & 1 zoster vaccine recipients experienced a 2nd evaluable HZ case – recurrent episode data not included in efficacy analyses

(Source: STN 125123, Protocol 004 Tables 7-1, 7-52)

9.4 Endpoint Results

Table 9-5 HZ Cases† and Population Subgroups Used in Statistical Analyses

	Description	N	% of study population	Placebo	Zoster vaccine	Placebo w/HZ	Zoster vaccine w/HZ	Total w/HZ
ITT	All randomized subjects - randomized just prior to vaccination	38,546	100%	19,276	19,270	660	321	981
	HZ by PCR	--	--	--	--	616	299	915
	HZ by virus culture	--	--	--	--	8	2	10
	HZ by CEC adjudication	--	--	--	--	36	20	56
MITT*	Followed ≥ 30 days postvaccination and did not develop evaluable cases of HZ w/in 30 days postvaccination	38,501	99.9%	19,247	19,254	642	315	957
	Excluded from MITT – HZ w/in 30 days	--	--	--	--	18	6	24
	Excluded from MITT: Discontinued w/in 30 days	--	--	11	10	--	--	--
MITT2	Followed ≥ 30 days postvaccination and did not develop HZ per Clinical Adjudication Committee (CEC) w/in 30 days postvaccination	38,504	99.9%	19,249	19,255	626	332	958
	Excluded from MITT2– HZ w/in 30 days	--	--	--	--	16	5	21
	Excluded from MITT2: Discontinued w/in 30days	--	--	11	10	--	--	--

* MITT is the primary efficacy analyses population
†Evaluable cases of HZ were determined by protocol defined hierarchical algorithm (see section 6.1) except in MITT2 population. In MITT2, all evaluable cases of HZ cases were determined based upon clinical diagnosis by CEC irrespective of PCR or viral culture results.

(Source: BLA 125123: Protocol 004 Tables 6-5, 11-2)

9.4.1 Primary and Secondary Endpoints

The results of the primary and secondary analyses are presented in Table 9-6. Burden of Illness (BOI), incidence of PHN, and incidence of HZ met the predefined criteria for success. The duration of clinically significant pain (20 days in the ZOSTAVAX™ group and 22 days in the placebo group) met the predefined statistical criteria for success ($p < 0.05$) however the clinical significance is unclear. The SIADL analysis did not meet the pre-defined criteria for success.

Table 9-6 Summary of Primary and Secondary Endpoint Results and Analyses

		Endpoint	Point Estimate (95% CI)	Additional related analyses and comments
Co-Primary	1	Herpes Zoster Burden of Illness (BOI) $VE_{BOI} = HZ\ BOI_{PLACEBO} - HZ\ BOI_{VACCINE}$	61.1% (51.1, 69.1)	Based upon pain scale (0-10, 10 = worst pain) Stratified by age group Using total follow-up times as weights All scores (0-10) Days 0-30; Scores ≥3 after Day 30 Treatment-by-age interaction: p=0.266
	2	Incidence of Post-herpetic neuralgia (PHN) $VE_{PHN} = PHN_{PLACEBO} - PHN_{VACCINE} / PHN_{PLACEBO}$	66.5% (47.5, 79.2)	27 PHN cases in vaccine group 80 PHN cases in placebo group Treatment-by-age interaction: p-value > 0.999
Secondary	1	Incidence of Herpes Zoster $VE_{HZ} = HZ_{PLACEBO} - HZ_{VACCINE} / HZ_{PLACEBO}$	51.3% (44.2, 57.6)	315 evaluable[1] cases HZ in vaccine group 642 evaluable[1] cases HZ in placebo group VE_{HZ} in 60-69 yr. old strata = 63.9% VE_{HZ} in ≥ 70 yr. old strata = 37.6%
	2	Duration of clinically significant pain[3]		20 days in zoster vaccine group 22 days in placebo group p-value <0.001 (MITT) p-value = 0.041 (Evaluable HZ)
	3	Substantial Interference with Activities of Daily Living[4] Above and Beyond VE_{HZ} SADLI = 1– Relative Risk SADLI / Relative Risk HZ		p-value = 0.341 Does not include vaccine effect on HZ incidence, unlike the other major efficacy endpoints Treatment-by-age interaction: p-value = 0.696

[1]Not included in efficacy analyses: Evaluable HZ cases w/in 30 days post-vaccination (6 cases in vaccine recipients vs. 18 cases in placebo groups)
[3] Clinically significant pain: Worst daily pain ≥3 after HZ rash onset until worst daily pain <3 for remainder of follow-up, up to 6 months following HZ rash onset. This was set at 0 for subjects who did not develop HZ.
[4] ADLI score ≥ 2 (1-10 pt.-scale, 10 = max. score) for ≥ 7 days during 6-mo. follow-up after HZ rash onset: General Activity, Mood, Walking ability, Normal work, Relations w/ others, Sleep and Enjoyment of life categories.
(Source: STN 125123; Protocol 004 Tables 7-4, 7-5, 7-9; Section 7.1)

The following table shows the effect of ZOSTAVAX™ as compared to placebo on incidence of HZ, incidence of PHN and BOI during the 5 hears postvaccination. These analyses were not prespecified.

Table 9-7 Durability of ZOSTAVAX™ Effect on Major Efficacy Endpoints (MITT)

Years On Study	Zoster Vaccine (N = 19270)				Placebo (N = 19276)				Vaccine Efficacy: (95% CI)†
Annual Incidence of Evaluable HZ Cases[1]									
	n	m	Follow-Up Time (Person-Years)	HZ Incidence (Per 1000 Person-Years)	n	m	Follow-Up Time (Person-Years)	HZ Incidence (Per 1000 Person-Years)	HZ Incidence
1	76	19254	19132	3.972	201	19247	19081	10.534	0.623 (0.507, 0.714)
2	103	18994	18827	5.471	194	18915	18679	10.386	0.473 (0.328, 0.589)
3	98	18626	14505	6.756	171	18422	14327	11.936	0.434 (0.270, 0.563)
4	35	9942	5412	6.467	70	9806	5325	13.145	0.508 (0.252, 0.682)
5	3	1906	327	9.183	6	1856	324	18.500	0.504 (-1.324, 0.920)
Overall	315	19254	58203	5.412	642	19247	57736	11.120	0.513 (0.442, 0.576)
Annual Incidence of PHN[1]									
	n	m	Follow-Up Time (Person-Years)	HZ Incidence (Per 1000 Person-Years)	n	m	Follow-Up Time (Person-Years)	HZ Incidence (Per 1000 Person-Years)	PHN Incidence
1	5	19254	19132	0.261	33	19247	19081	1.729	0.849 (0.610, 0.954)
2	8	18994	18827	0.425	22	18915	18679	1.178	0.639 (0.159, 0.861)
3	10	18626	14505	0.689	17	18422	14327	1.187	0.419 (-0.344, 0.762)
4	3	9942	5412	0.554	7	9806	5325	1.315	0.578 (-0.847, 0.930)
5	1	1906	327	3.061	1	1856	324	3.083	0.007 (-76.930, 0.987)
Overall	27	19254	58203	0.464	80	19247	57736	1.384	0.665 (0.475, 0.792)
Estimated HZ BOI‡ Based on AUC Scale Over 6 Months of Follow-Up After HZ Rash Onset[2]§									
	n	m	Total Follow-Up Time (Person-Years)	Estimated HZ Pain BOI‡	n	m	Total Follow-Up Time (Person-Years)	Estimated HZ Pain BOI‡	HZ Pain BOI
1	76	19254	19132	0.427	201	19247	19081	2.075	0.794 (0.682, 0.867)
2	103	18994	18827	0.801	194	18915	18679	1.661	0.518 (0.266, 0.683)
3	98	18626	14505	0.809	171	18422	14327	1.482	0.454 (0.193, 0.631)
4	35	9942	5412	0.367	70	9806	5325	1.007	0.635 (0.246, 0.824)
5	3	1906	327	0.094	6	1856	324	0.375	0.748 (0.190, 0.922)
Overall	315	19254	58203	2.208	642	19247	57736	5.682	0.611 (0.511 0.691)

[1]Calculated: 1 - ratio of observed HZ incidence rates in zoster vaccine group & placebo group. CI based on exact conditional procedure.

[2] AUC in 6 mos. follow-up after HZ rash onset: (1) patient-reported data on HZ between rash onset & first patient interview collected on IZIQ; (2) excludes pain scores <3 that occur on ≥ 2 consecutive visits > 30 days after rash onset; and (3) included recurrent pain with score ≥3 beyond 30 days after HZ rash onset.

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

§ VE calculated as a weighted average of observed zoster 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.

MITT population: randomized, followed ≥ 30 days postvaccination, w/o evaluable HZ w/in days 0-30 postvaccination.

N = # subjects randomized n = # evaluable HZ cases in time period m = # MITT subjects followed in time period

(Source: STN 125123, Protocol 004 Table 7-45)

Effect of Age on Vaccine Efficacy

As noted in Table 9.6, age is the most consistently and strongly associated factor in explaining vaccine response. Older subjects (≥70 years old) had lower vaccine efficacy in prevention of HZ, and higher rates of HZ in both vaccine and placebo groups as compared to the younger subjects (60-69 years old). The following tables (Table 9.8 and 9.9) show the effect of age on incidence of HZ.

Table 9-8 Incidence of evaluable HZ case (MITT population)

Age*	Placebo (N=19247)				Zoster Vaccine (N=19254)			
	# subjects	# subjects with HZ	Total follow-up time (yrs)	Incidence rate (1000 person yrs)	# subjects	# subjects with HZ	Total follow-up time (yrs)	Incidence rate (1000 person yrs)
59-64	5198	153	15384	9.945	5216	54	15693	3.441
65-69	5158	181	15569	11.626	5154	68	15630	4.351
70-74	4560	158	13814	11.438	4545	89	13830	6.435
75-79	2999	103	9105	11.312	3076	67	9329	7.182
80-84	1097	39	3189	12.230	1063	31	3172	9.773
85-89	210	7	605	11.570	181	5	498	10.040
90+	25	1	70	14.286	19	1	51	19.608
Total	19247	642	57736	11.120	19254	315	58203	5.412
*Age at randomization								

(Source: FDA analysis of HZ datasets)

Table 9-9 Effect of Major Efficacy Endpoints, MITT Population

Zoster Vaccine (N = 19270)					Placebo (N = 19276)				Vaccine Efficacy for HZ BOI (95% CIs)
Effect of Age on BOI – AUC									
	n	m	Follow-Up Time (Person-Years)	HZ BOI‡	n	M	Follow-Up Time (Person-Years)	HZ BOI‡	
60-69 yrs.	122	10370	31323	1.495	334	10356	30953	4.334	0.655 (0.515, 0.755)
≥ 70 yrs.	193	8884	26881	3.471	308	8891	26783	7.781	0.554 (0.399, 0.669)
Effect of Age on PHN Incidence									
	n	m	Follow- Up Time (Person-Years)	Incidence of PHN† (1000 Person-Yrs.)	n	M	Follow-Up Time (Person-Years)	Incidence of PHN† (1000 Person-Yrs.)	Vaccine Efficacy for PHN Incidence (95% CI)‡ ‡
60-69 yrs.	8	10370	31323	0.255	23	10356	30953	0.743	0.656 (0.204, 0.867)
≥ 70 yrs.	19	8884	26881	0.707	57	8891	26783	2.128	0.668 (0.433, 0.813)
Effect of Age on HZ Incidence									
	n	m	Follow- Up Time (Person-Years)	Incidence of HZ (1000 Person-Yrs.)	n	M	Follow-Up Time (Person-Years)	Incidence of HZ (1000 Person-Years)	Vaccine Efficacy for HZ Incidence (95% CI)† †
60-69 yrs.	122	10370	31323	3.895	334	10356	30953	10.791	0.639 (0.555, 0.709)
≥70 yrs.	193	8884	26881	7.180	308	8891	26783	11.500	0.376 (0.250, 0.481)

†Protocol-defined AUC: (1) incorporates patient-reported data on HZ between rash onset and 1st interview collected on IZIQ; (2) excludes pain scores < 3 that occur on 2 or more consecutive visits > 30 days after rash onset; and (3) included recurrent pain with score ≥ 3 after 2 consecutive visits with worst pain scores <3 beyond 30 days after HZ rash onset.

††1 minus the ratio of estimated incidence rates of HZ in zoster vaccine group and placebo group. CI was constructed based on the exact conditional procedure.

‡Weighted average of observed BOI stratified by age group (60-69 and ≥70 yrs) w/ weights proportional to total follow-up time in each age group.

‡‡ Calculated as 1 minus the ratio of estimated incidence rate of PHN between the zoster vaccine group and the placebo group. The CI was constructed based on the exact conditional procedure stratified by 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 was constructed based on the large sample approximation under the fixed-number-of-events design.

MITT-2: All randomized subjects followed ≥30 days postvaccination and did not develop (per clinical adjudication) w/in 30 days postvaccination.

Subjects considered to be immunosuppressed if immunosuppressed at study entry (resulting from a disease), at rash onset, or at time of termination.

N = Number of subjects randomized n = Number of evaluable HZ cases in specified population m = Number of subjects w/ active follow-up for HZ surveillance in ITT population AUC = Area under the curve HZ = Herpes zoster

BOI = Burden of illness IZIQ = Initial zoster impact questionnaire ITT = Intention-to-treat CI = Confidence interval

(Source: BLA 125123; Protocol 004 Tables 11-22, 11-37 & 7-10)

9.4.2 SELECTED TERTIARY EFFICACY ENDPOINTS

Tertiary Endpoint: PHN Using Alternative Definitions

Table 9-10 Incidence of PHN Using Alternative PHN Definition - MITT Population

PHN defined by Cutoff Day (After Rash Onset)	Zoster Vaccine (m = 19245) Follow-Up (person-yrs.) = 58203		Placebo (m = 19247) Follow-Up (person-yrs.) = 57736		Vaccine Efficacy with Respect to PHN Point Estimate (95% CI) ‡
	n	Incidence Rate of PHN† /1000 Person-Years	n	Incidence Rate of PHN† /1000 Person-Years	
30	81	1.393	196	3.393	0.589 (0.466, 0.687)
60	45	0.774	113	1.956	0.604 (0.436, 0.726)
90	27	0.464	80	1.384	0.665 (0.475, 0.792)
120	17	0.292	54	0.934	0.687 (0.452, 0.830)
182	9	0.155	33	0.571	0.729 (0.421, 0.886)

†Weighted average of the observed incidence rate stratified by age group (60 to 69 and ≥ 70 years) 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 zoster vaccine and placebo groups. The CI was constructed based on the exact conditional procedure stratified by age group.
PHN for the co-primary endpoint was defined as any HZ-associated pain rated ≥ 3 (on a 0 to 10 scale) persisting or appearing ≥ 90 days after the HZ rash onset.
Alternative PHN definitions were pain ≥ 3 persisting or appearing more than 30, 60, 120, or 182 days after HZ rash onset.
MITT: All randomized subjects who were followed ≥ 30 days postvaccination and did not develop evaluable cases of HZ (per the hierarchical algorithm specified in Protocol Amendment 6) within the first 30 days postvaccination.
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. PHN = Postherpetic neuralgia. HZ = Herpes zoster. MITT = Modified intention-to-treat. CI = Confidence interval.

(Source: BLA 125123; 5.3.5.1.1.4 Table 7-15)

If the Co-Primary Endpoint in Protocol 004 (PHN) had not been redefined during the course of the study as reduction in the incidence of PHN occurring or persisting at Day 90, rather than at Day 30 as originally designated, following HZ rash onset, the study would have failed the pre-specified criterion for success. The pre-specified success criterion required that the point estimate for reduction in PHN incidence be > 62%. Based upon sponsor-conducted sensitivity analyses the study would have failed using either 30 or 60 days as the cutoff defining PHN persistence or occurrence.

Given that the majority of cases of PHN resolve completely within a few weeks after HZ rash onset, the use of a 90-day cutoff for evaluation of treatments for PHN appears useful. It is not clear that a 90-day cutoff is the most appropriate in a preventive study which seeks to evaluate the overall burden of illness due to PHN experienced in the study population. In the latter case it would seem that capturing the largest number of PHN cases would be informative as to the complete burden of illness due to PHN and also more sensitive to differences between treatment groups.

Tertiary Endpoint: Efficacy and Immunogenicity of 3 Consistency Lots of the Vaccine
Vaccine efficacy among 3 consistency lots was assessed by the estimation of pairwise ratios in the clinical endpoints of HZ pain BOI, the incidence of PHN, and the incidence of HZ among the 3 consistency lots using 90% CIs for lot-to-lot comparisons. No statistically significant differences were found in the analysis of these data. The immunogenicity results for each pair of consistency lots are shown in table 9-11.

Table 9-11 Fold Rise in gpELISA Titers 6 Weeks Postvaccination by Vaccine Lot

Consistency Lot	Vaccine Lot	Zoster Vaccine (N = 691)			
		n	m	GMF	95% CI
1	1562W-E 471	73	78	1.7	(1.5, 2.0)
2	1563W-E 472	76	82	1.8	(1.5, 2.1)
3	1564W-E 473	93	97	1.9	(1.6, 2.3)
1	1588W-G 479	138	146	1.7	(1.5, 1.9)
2	1589W-G 480	141	147	1.6	(1.4, 1.8)
3	1590W-G 481	134	141	1.6	(1.4, 1.8)

N = Number of subjects vaccinated in the CMI Substudy.
n = Number of subjects contributing to immunogenicity analysis.
m= Number of subjects vaccinated in CMI Substudy in each lot category.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
CMI = Cell mediated immunity.
GMF = Geometric mean fold rise.
CI = Confidence interval.

Source: STN 125123, Protocol 004, Table 11-118

Tertiary Endpoint: Effect of a Reduction in Plaque-Forming Unit (PFU) Content Over time on Vaccine Efficacy

The evaluation of the effects of potency on vaccine efficacy included all clinical lots. When used as a regression parameter, vaccine potency was found not significant in the analyses of each of the three efficacy endpoints (HZ incidence, PHN incidence and BOI scores). In fact the Cox Regression model indicated age as the most consistently significant explanatory variable for efficacy effect.

Comparison of efficacy by clinical lots is made difficult by the large number of clinical lots (twelve) and in many cases, the relatively small numbers of events in each clinical lot group. Small losses in efficacy measures for BOI scores and PHN incidence is seen in unaged clinical lots (046, 047, 048) as compared to the remaining aged lots, but this observation is of uncertain clinical significance.

Table 9-12 Summary of HZ BOI Based on the Protocol-Defined AUC Scale† Over 6 Months of Follow-Up After HZ Rash Onset by Vaccine Lot (MITT Population)

Vaccine Lot	Dose Potency When Shipped (PFU/dose)	Zoster Vaccine (N=19270)				
		n	m	Total Follow-Up (Person-Years)	Observed HZ BOI	95% CI
1535W-E 046	52018	6	278	1097	4.261	(2.239, 8.108)
1536W-E 047	61833	7	278	1119	6.943	(2.729, 17.660)
1537W-E 048	50063	8	279	1133	4.020	(1.697, 9.522)
1553W-E 462	37273	4	326	1277	1.712	(0.393, 7.458)
1534W-E 463	42403	8	326	1282	3.284	(2.078, 5.190)
1535W-E 464	34362	7	326	1266	2.160	(0.950, 4.910)
1562W-E 471	27633	56	2906	9764	3.170	(2.334, 4.305)
1563W-E 472	26371	63	2903	9766	2.168	(1.630, 2.882)
1564W-E 473	32588	53	2901	9745	2.658	(1.927, 3.665)
1588W-G 479	21480	35	2912	7271	1.543	(1.136, 2.095)
1589W-G 480	26218	38	2908	7238	1.954	(1.169, 3.266)
1590W-G 481	24931	30	2911	7247	2.193	(1.331, 3.614)

†Protocol-defined AUC: (1) incorporates patient-reported data on HZ between rash onset and the first patient interview collected on IZIQ; (2) excludes pain scores <3 that occur on 2 or more consecutive visits more than 30 days after rash onset; and (3) included recurrent pain with score ≥ 3 after 2 consecutive visits with worst pain scores <3 beyond 30 days after HZ rash onset.
The MITT population included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop evaluable cases of HZ (per the hierarchical algorithm specified in Protocol Amendment 6) within the first 30 days postvaccination.
N = Number of subjects randomized in the vaccination group
n = Number of evaluable HZ cases in the MITT population
m = Number of subjects in the MITT population.
HZ = Herpes zoster
AUC = Area under the curve
CI = Confidence interval
BOI = Burden of illness
MITT = Modified intention-to-treat
IZIQ = Initial zoster impact questionnaire

(Source: STN 125123, Protocol 004 Table 11-71)

Table 9-13 Summary of Incidence of PHN by Vaccine Lot (MITT Population)

Vaccine Lot	Dose Potency When Shipped (PFU/dose)	Zoster Vaccine (N = 19270)				
		n	M	Total Follow-Up (Person-Years)	Observed Incidence Rate of PHN (Per 1000 Person-Years)	95% CI
1535W-E 046	52018.5	2	278	1097	1.823	(0.221, 6.586)
1536W-E 047	61833.5	2	278	1119	1.787	(0.216, 6.457)
1537W-E 048	50063.0	0	279	1133	0.000	(0.000, 3.255)
1553W-E 462	37273.0	0	326	1277	0.000	(0.000, 2.889)
1534W-E 463	42403.5	2	326	1282	1.560	(0.189, 5.635)
1535W-E 464	34362.5	0	326	1266	0.000	(0.000, 2.914)
1562W-E 471	27633.5	5	2906	9764	0.512	(0.166, 1.195)
1563W-E 472	26371.5	2	2903	9766	0.205	(0.025, 0.740)
1564W-E 473	32588.0	4	2901	9745	0.410	(0.112, 1.051)
1588W-G 479	21480.5	3	2912	7271	0.413	(0.085, 1.206)
1589W-G 480	26218.0	3	2908	7238	0.414	(0.085, 1.211)
1590W-G 481	24931.0	4	2911	7247	0.552	(0.150, 1.413)

MITT: All randomized subjects who were followed ≥ 30 days postvaccination and did not develop evaluable cases of HZ (per the hierarchical algorithm, Protocol Amendment 6) within the first 30 days postvaccination.
N = Number of subjects randomized.
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 HZ = Herpes zoster
PHN = Postherpetic neuralgia MITT = Modified intention-to-treat
CI = Confidence interval

(Source: STN 125123, Protocol 004, Table 11-72)

Table 9-14 Incidence of Evaluable HZ Cases by Vaccine Lot (MITT Population)

Vaccine Lot	Dose Potency When Shipped (PFU/dose)	Zoster Vaccine (N = 19270)					
		n	m	Total Follow-Up (Person-Years)	Average Follow-Up (Days)	Observed Incidence Rate of HZ (Per 1000 Person-Years)	95% CI
1535W-E 046	52018.5	6	278	1097	1441	5.469	(2.007, 11.904)
1536W-E 047	61833.5	7	278	1119	1470	6.256	(2.515, 12.890)
1537W-E 048	50063.0	8	279	1133	1483	7.060	(3.048, 13.911)
1553W-E 462	37273.0	4	326	1277	1430	3.133	(0.854, 8.022)
1534W-E 463	42403.5	8	326	1282	1436	6.240	(2.694, 12.295)
1535W-E 464	34362.5	7	326	1266	1418	5.530	(2.223, 11.394)
1562W-E 471	27633.5	56	2906	9764	1227	5.736	(4.333, 7.448)
1563W-E 472	26371.5	63	2903	9766	1229	6.451	(4.957, 8.254)
1564W-E 473	32588.0	53	2901	9745	1227	5.439	(4.074, 7.114)
1588W-G 479	21480.5	35	2912	7271	912	4.814	(3.353, 6.695)
1589W-G 480	26218.0	38	2908	7238	909	5.250	(3.715, 7.206)
1590W-G 481	24931.0	30	2911	7247	909	4.140	(2.793, 5.910)

MITT: All randomized subjects who were followed ≥ 30 days postvaccination and did not develop evaluable cases of HZ (per the hierarchical algorithm, Protocol Amendment 6) within the first 30 days postvaccination.
N = # subjects randomized n = # of evaluable HZ cases m = # subjects in the MITT population
HZ = Herpes zoster MITT = Modified intention-to-treat CI = Confidence interval

(Source: STN 125123, Protocol 004, Table 11-73)

Tertiary Endpoint: VZV-Specific Immune Responses

Immunogenicity data (both humoral and cell-mediated) are from subjects enrolled in the Cell-mediated Immunity Substudy (CMI) and included results of gpELISA, Responder Cell Frequency (RCF) and IFN-γ ELISPOT assays. The gpELISA assay appears to be the most informative in terms of magnitude of response as well as differences between treatments groups.

Measures of cellular immunity, RCF and IFN-γ ELISPOT data, are limited by lower the relatively lower magnitude of response and relatively higher variability in assay results as well as the technical complexity of collecting and handling the samples. The data derived from RCF and ELISPOT at this point do not appear to add significantly to the information derived from gpELISA data and will not be discussed further.

Primary analyses are based upon a per-protocol population, excluding those with insufficient sample, sample not obtained in designated time window, high background, invalid sample, storage or handling problems and invalid assay results for the RCF and IFN- γ ELISPOT and gpELISA assays. There were no large notable differences between treatment groups in the proportion of data in each assay that was excluded from the per-protocol analysis. Antibodies to VZV were assessed 6 weeks following immunization with ZOSTAVAX™ or placebo using a gpELISA assay.

Table 9-15 gpELISA Titers in CMI Substudy Participants 6 Weeks Postvaccination

Endpoint	Zoster Vaccine (N=691; n = 655-678) Observed Response (95% CI)		Placebo (N=704; n = 673-691) Observed Response (95% CI)	
Day 0 (gpELISA units/mL)				
	n = 678		n = 691	
% ≥200	60.5%	(56.7%, 64.2%)	64.4%	(60.7%, 68.0%)
GMT	278.8	(258.0, 301.4)	291.0	(269.7, 314.0)
6 Weeks Postvaccination (gpELISA units/mL)				
	n = 667		n = 684	
% ≥200	83.4%	(80.3%, 86.1%)	64.6%	(60.9%, 68.2%)
GMT	474.7	(441.5, 510.5)	291.4	(269.3, 315.3)
6 Weeks Postvaccination (Fold Rises from Day 0)				
	n = 655		n = 673	
% ≥2fold	35.7%	(32.1%, 39.5%)	7.1%	(5.3%, 9.3%)
% ≥3fold	16.9%	(14.2%, 20.0%)	2.5%	(1.5%, 4.0%)
% ≥4fold	10.7%	(8.4%, 13.3%)	1.0%	(0.4%, 2.1%)
% ≥5fold	7.0%	(5.2%, 9.3%)	0.4%	(0.1%, 1.3%)
Geometric Mean Fold Rise	1.7	(1.6, 1.8)	1.0	(1.0, 1.0)
90 Percentile of Fold Rise	4.2		1.7†	
95 Percentile of Fold Rise	6.4		2.4‡	

†Percent of subjects in vaccine group with a fold rise above this cutoff was 44.3% [95% CI= (40.4%, 48.2%)]
‡Percent of subjects in vaccine group w/ fold rise above this cutoff was 27.9% [95% CIs: 24.5%, 31.5%]
N = # subjects vaccinated in CMI substudy n = # subjects contributing to immunogenicity analysis.
gpELISA - Glycoprotein enzyme-linked immunosorbent assay
GMT - Geometric mean titer CI - Confidence interval.

(Source: STN 125123, Protocol 004 Table 7-64)

The persistence of gpELISA titers from Day 0 to 3 years postvaccination is shown in the following table.

Table 9-16 Persistence of gpELISA Titers Among the CMI Substudy

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

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

(Source: STN 125123, Protocol 004, Table 7-71)

Prevaccination titers, age and timing of the 6-week blood sample had statistically significant effects on the gpELISA responses at 6 weeks postvaccination.

Gender, study site and the vaccine potency subjects received did not have statistically significant effects. The effect of age was more obvious in the lowest prevaccination titer category: the fold rises were higher in the younger age group than in the older age group when prevaccination titer was <100, but more similar when prevaccination titers were ≥ 100.

Overall, zoster vaccine recipients with relatively lower gpELISA titers at Day 0 appeared to have relatively lower titers but higher fold rises at 6 weeks postvaccination.

In the zoster vaccine group, the fold rises at 6 weeks postvaccination appeared to be comparable between males and females. In the placebo group, no increase of fold rises was observed in any of the subgroups.

Zoster vaccine recipients had comparable gpELISA titers at 6 weeks postvaccination, regardless of the vaccine lot they received.

Tertiary Endpoint: Immune Responses as Correlates of Protection

Subjects who did not develop HZ had higher gpELISA titers at 6 weeks postvaccination compared with the subjects who developed HZ. This difference held true for both the placebo as well as the zoster vaccine group, although the number of subjects who developed HZ was very small in the zoster vaccine group.

Table 9-17 Immune Responses Among CMI Substudy Participants by HZ Incidence Status

Endpoint	Subject Cohort (HZ Status After 6-Week Blood Sampling Date)	Zoster Vaccine (N=691) n	Observed Response	95% CI	Placebo (N=704) n	Observed Response	95% CI
gpELISA							
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
GMFR 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 were excluded from this analysis.
N = Number of subjects vaccinated in the CMI Substudy.
n = Number of subjects contributing to the immunogenicity analysis.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
VZV = Varicella-zoster virus.
CMI = Cell mediated immunity. GMT = Geometric mean titer. GMFR = Geometric Mean Fold-Rise
CI = Confidence interval. HZ = Herpes zoster. .

(Source: STN 125123, Protocol 004 Tables 7-75 through 7–77)

Table 9-18 Risk of HZ by 6 Week gpELISA Titer

gpELISA Titer	Placebo % (n/N)	Zoster % (n/N)
≤100	5.43% (5/92)	0.0% (0/24)
100-200	4.08% (6/147)	3.49% (3/86)
200-300	4.24% (5/118)	2.78% (3/108)
300-400	5.41% (6/111)	0.83% (1/121)
400-500	0.0% (0/14)	5.56% (1/18)
500-600	0.0% (0/32)	0.0% (0/31)
600-700	6.25% (1/16)	0.0% (0/34)
700-800	0.0% (0/20)	0.0% (0/35)
800-900	0.0% (0/17)	0.0% (0/29)
900-1000	0.0% (0/12)	0.0% (0/23)
≥1000	0.0% (0/94)	0.68% (1/146)
Total	3.42% (23/673)	1.37% (9/655)

N = # subjects with titer n = # subjects w/ titer & developing HZ during study

(Source: FDA analysis of immunogenicity datasets)

The interpretation of these estimates is limited by the small number of HZ cases. Although the number of vaccinated subjects in the CMI substudy who developed HZ was small (9) it appears that those individuals with higher postvaccination gpELISA titer were less likely to develop HZ.

Tertiary Endpoint: Impact of HZ and Its Complications on Quality of Life of Older Persons

SF-12 Health Survey and EuroQoL Visual Analog Scale did not reveal differences between groups.

Increases in ZBPI worst pain scores were generally associated with decreases in SF-12 Physical and Mental Health summary scales, and decreases in EuroQoL-measured general health states.

Tertiary Endpoint: Natural History of Herpes Zoster in Older Persons

981 study participants overall (32 CMI substudy participants) were diagnosed w/ HZ postvaccination.

The most commonly affected dermatome was that of the first branch of the trigeminal nerve. In general, the reduction in HZ provided by the vaccine was seen across dermatomes. There were no particular pattern in the differences between treatment groups with respect to affected dermatomes, but the number of subjects with any particular affected dermatome was small.

In the ITT population, the zoster vaccine group appeared to have a slightly lower incidence of prodromal pain (57%) when compared to the incidence in the placebo group (63%). The mean worst prodromal pain score and the mean duration appeared similar between the two vaccination groups. These comparisons are similar to those for each age group.

HZ complications
Most common complications (reported in ≥ 10% in at least one treatment group) were prodromal pain, acute pain, any pain after 30 days after rash onset, and allodynia. Other complications that were reported with frequencies of ≥1% in at least one vaccination group were disseminated rash, scarring, motor neuron palsies, sensory loss, ptosis, and vision impairment.

There are no clear differences between groups in the rates of the various reported complications.

In terms of life-threatening complications, pneumonitis was reported to occur in 0.5% of the cases in the placebo group, no cases of pneumonitis were reported to occur in the ZOSTAVAX™ group; cerebral dysfunction was reported to occur in one subject in the placebo group; and meningoencephalitis was reported to occur in one subject in the vaccine group.

Immune status
5.3% of the zoster vaccine group and 2.4% of the placebo group subjects were immunosuppressed at HZ onset as demonstrated in the following table:

Table 9-19 Immune Status at Onset of Herpes Zoster - Evaluable Cases (ITT Population)

	Zoster Vaccine (N = 19270)		Placebo (N = 19276)	
	n/m	(%)	n/m	(%)
Immunosuppressed at Onset of HZ	17/320	(5.3)	16/659	(2.4)
	n	(%)†	N	(%)†
Subjects receiving corticosteroids	5	(29.4)	6	(37.5)
Subjects receiving chemotherapy for neoplastic disease	4	(23.5)	6	(37.5)
Subjects received transplantation	1	(5.9)	1	(6.3)
Subjects with malignancy	9	(52.9)	9	(56.3)
Other	7	(41.2)	3	(18.8)

†% was calculated based on number of subjects who were immunosuppressed.
N = # subjects randomized m = # subjects responding to question in respective category
n = # subjects in respective category HZ = Herpes zoster ITT=Intention-to-treat
Other = Methotrexate, purineth [sic], radiation therapy, neoplasm, infection, emphysema, polymyalgia rheumatica, or pulmonary fibrosis.

(Source: STN 125123, Protocol 004 Table 11-94)

Evaluable Herpes zoster occurred in 981 study participants including 32 of the CMI Substudy participants.

As mentioned in Table 9-17, subjects who later developed HZ appeared to have generally lower immune responses as measured by gpELISA at 6 weeks postvaccination compared to subjects who did not develop HZ, although the number of zoster vaccine recipients in the CMI Substudy who developed HZ was small. The overall immune response following HZ was similar between treatment groups.

As shown in Table 9-20, gpELISA titers were highest from 14-84 days after HZ rash onset. Responses decreased over time.

Table 9-20 gpELISA Responses 6 Weeks Following Occurrence of Evaluable HZ

Endpoint	Time Point	Zoster Vaccine (N=2276)			Placebo (N=2278)		
		n	Observed Response	95% CI	n	Observed Response	95% CI
GMT	Visit 1*	270	672.9	(557.9, 811.7)	558	743.5	(650.5, 849.9)
	3 Weeks	251	2674.4	(2316.7, 3087.3)	544	3374.2	(3053.3, 3728.9)
	6 Weeks	281	2042.1	(1805.2, 2309.9)	599	2260.0	(2070.4, 2466.8)
	12 Months	225	523.3	(468.0, 585.0)	470	597.0	(552.3, 645.2)
	24 Months	115	464.7	(384.1, 562.2)	272	484.2	(433.7, 540.7)
	36 Months	57	361.4	(287.2, 454.8)	152	493.5	(420.6, 579.1)
Geometric Mean Fold Rises from Day 0	3 Weeks	225	4.2	(3.4, 5.1)	485	4.6	(3.9, 5.3)
	6 Weeks	253	3.2	(2.6, 3.9)	536	3.1	(2.7, 3.5)
	12 Months	203	0.8	(0.6, 1.0)	419	0.9	(0.8, 1.0)
	24 Months	104	0.8	(0.6, 1.0)	246	0.7	(0.6, 0.9)
	36 Months	52	0.7	(0.5, 1.1)	136	0.8	(0.7, 1.0)

Visit 1 occurred within 14 days of HZ rash onset.
N = # subjects vaccinated (San Diego, Denver) n = # evaluable HZ cases in immunogenicity analysis.
VZV = Varicella-zoster virus. gpELISA = Glycoprotein enzyme-linked immunosorbent assay
GMT = Geometric mean titer CMI = Cell mediated immunity CI = Confidence interval
IFN = Interferon N/A = Not applicable, i.e., CI not calculated when n<5.

(Source: STN 125123, Protocol 004, Table 7-72 through 7-74)

The immune response to vaccination (CMI substudy subjects) and the response of both ZOSTAVAX™ and placebo vaccinated subjects to naturally acquired HZ disease are shown in the following table. Both gpELISA GMT and gpELISA foldrise at 6 weeks following onset of rash in HZ cases were higher (non-overlapping CIs) than the results seen 6 weeks postvaccination in the ZOSTAVAX™ vaccine group.

Table 9-21 Comparison of Immunogenicity Results: 6 weeks postvaccination in ZOSTAVAX™ Recipients (CMI Substudy) And 6 weeks following HZ in ZOSTAVAX™ & Placebo Recipients (MITT)

	Postvaccination (zoster vaccine)			Following Evaluable HZ					
	CMI Substudy			Zoster Vaccine			Placebo		
	(N=691)			(N=2276)			(N=2278)		
	N	Observed Response	95% CI	n	Observed Response	95% CI	n	Observed Response	95% CI
gpELISA									
GMT	667	474.7	441.5, 510.5	281	2042.1	1805.2, 2309.9	599	2260.0	2070.4, 2466.8
GMFR from Day 0	655	1.7	1.6, 1.8	253	3.2	2.6, 3.9	536	3.1	2.7, 3.5

N = number of subjects vaccinated at the CMI substudy sites (Denver and Colorado)
CMI substudy: n = number of subjects with available data
Evaluable HZ: n = number of evaluable HZ cases with available data
* GMFR = geometric mean fold rise

(Source: STN 125123, Protocol 004, Tables 7-71 and 7-74)

Recurrent HZ
3 subjects, 1 in zoster vaccine group and 2 in the placebo group, developed multiple evaluable cases of HZ. All cases were PCR positive for wildtype VZV. Only data from the first evaluable HZ case was used in study analyses.

Table 9-22 Multiple Cases of Herpes Zoster (ITT)

Allocation Number	Number of Episodes	Study Day[1]	Immune Status At Onset of HZ	Lesion Number	Severity-by-Duration of Pain (AUC †)	Days to to Pain <3‡	PHN Case§
Zoster Vaccine							
1050020	2	959	Unknown	11 - 20	252.5	37	No
		1331	Immunosuppressed	> 100	464.5	70	No
Placebo							
5780481	2	576	Normal	1 to 10	0	10	No
		1338	Normal	21 to 50	48.5	14	No
5960382	2	215	Normal	11 to 20	55	10	No
		908	Normal	1 to 10	90	17	No

†Protocol-defined AUC:
(a) Patient-reported data on HZ pain between rash onset and first patient interview collected on IZIQ.
(b) Excludes pain scores 3 that occur more than 30 days after rash onset; and (3) included recurrent pain with score ≥3 after consecutive visits with "worst pain" scores <3 beyond 30 days after HZ rash onset.
‡Time from rash onset to attaining a persistent define in methods section worst pain score <3 on ZBPI.
§PHN defined as HZ-associated pain & discomfort ≥3 (0-10 scale) persisting or appearing ≥90 days after HZ rash onset.
[1]Relative day from vaccination
AUC = Area under the curve IZIQ = Initial Zoster impact questionnaire HZ = Herpes zoster.
ITT = Intention-to-treat PHN = Postherpetic neuralgia ZBPI = Zoster brief pain inventory
(Source: STN 125123, Protocol 004 Table 7-7)

Tertiary Endpoint: Safety Profile of Zoster Vaccine in Persons ≥ 60 years old

All vaccinated subjects were included in the safety analysis population

Baseline
Prior medical conditions and therapies within 90 days prior to vaccination appear similar between vaccine and placebo groups.

42-Day Safety Follow-Up
The only study-wide safety follow-up occurred at Day 42 postvaccination, utilized the Automated Telephone Reporting System (ATRS) and could occur at any time during the study, i.e., up to 4-5 years post-vaccination. Adverse events reported at the Day 42 safety follow-up were only counted in the Day 42 safety database and analyses if they occurred within 42 days following vaccination. Investigators could also enter follow-up information in the ATRS for study subjects at any time during the study.

Based upon information provided by the sponsor, adequate safety follow-up did not require participation in the planned Day 42 safety follow-up as described by Protocol 004. Although the protocol does not describe a hierarchical approach to safety monitoring, the sponsor considers complete safety follow-up for the purposes of this study based upon information from sources in the following order, occurring at any time during the study (up to ~4.5 years postvaccination): Vaccine Report Card (VRC), 42 Day ATRS entry by subject or by staff, report of staff follow-up but without Day 42 follow-up, report of an AE at any time, report of any contact within 60 days postvaccination.

Table 9-23 ATRS Safety Follow-Up at Day 42 (ITT Population; N=38,546)

	Number (%) of All Study Subjects
Of Those With Day 42 ATRS Data	**25,613 (66%)**
# subject who responded to ATRS as planned	21,117 (55%)
# subjects for whom staff called ATRS & entered data for subject	4,496 (11%)
AE Monitoring Cohort w/Day 42 ATRS Safety Follow-Up 601 / 6616 subjects (included in 2 ATRS categories above)	601 (1.6%) (9% of AE cohort)
Additional reports (≥6) for a subject after initial entry (not included in the 2 ATRS categories above)	1,240 (0.3%)
Of Those Without Day 42 ATRS Data	**12,994 (34%)**
AE Monitoring Substudy / Vaccine Report Cards (VRC) submitted	6,414 (17%)
Not in AE Monitoring Substudy - No VRC used	6,623 (17%)
Staff follow-up; no Day 42 ATRS entry / no VRC record	4,175 (11%)
ATRS generated FAX to staff but ATRS record lost	5 (0.0%)
Report of any contact within 60 days	1,107 (2.9%)
Report of an AE at any time	174 (0.5%)

(Source: STN 125123, Protocol 004 QUEST42 Datasets)

Table 9-24 shows the number of calls made by either subject or staff to the ATRS by time since vaccination.

Table 9-24 42 Day ATRS Safety Follow-Up by Source and Time Course

Days Postvaccination	Total Calls	# Subject Calls ATRS	#Staff calls to ATRS for subject
-5 – 0	1	1	0
1 – 28	14	12	2
29-42	79	10	69
43	116	15	101
44	17,758	17,248	510
45	1909	1,702	207
46	1124	987	137
47	614	477	137
48	521	434	87
49	324	193	131
50	325	213	112
51	820	0	820
52	393	1	392
53	266	0	320
54	265	0	265
55	230	0	230
56	250	0	250
57-70	1007	0	1007
71-84	235	0	235
85-98	92	0	92
99-126	74	0	74
127-182	79	0	79
183-365	191	0	191
366-730	386	1	385
731-1095	299	0	299

(Source: STN125123, Protocol 004 QUEST42 datasets)

Subjects who responded to the ATRS for Day 42 safety follow-up did so largely between Day 44 and Day 50 postvaccination. Investigators entered data for subject for the ATRS Day 42 safety follow-up for several years postvaccination.

It is not clear whether the large amount of underreporting is related to study subjects' difficulty understanding how to report to and/or use the ATRS system. It is not clear whether any corrective action was taken during the study to increase per-protocol reporting. It is noted that the ATRS program was significantly shortened during the study based upon subject comments.

The potential impact of different patterns of reporting on monitored parameters and study endpoints is unclear. There is no data submitted regarding subject compliance with monthly ATRS follow-up.

Premature Unblinding

Two placebo recipients were prematurely unblinded due to adverse events.

Table 9-25 Premature Unblinding Due to Adverse Events

Treatment	Study Day	Demographic Information	Reason for unblinding	Considered Serious AE?
Placebo	43	70 yr. old male	Fever, myalgia	No
Placebo	52	78 yr. old male	Goodpasture's glomerulonephritis	Yes

(Source: STN 125123; Protocol 004, Section 6.3)

Adverse events reported within 42 days of receipt of either ZOSTAVAX™ or placebo are shown in Table 9-26 and Table 9-27.

Table 9-26 Clinical Adverse Experiences Days 0-42

Routine Safety Monitoring Cohort	Zoster Vaccine		Placebo	
	(N = 15925)		(N = 16005)	
	N	(%)	n	(%)
Number of subjects	15925		16005	
Subjects with safety follow-up	15345	96.3	15468	96.6
Subjects without safety follow-up	580‡	3.6	537‡	3.4
Serious adverse experiences	191	1.24	213	1.38
Serious vaccine-related adverse experiences†	2	0.01	1	0.01
Died	11	0.07	14	0.09
Discontinued due to an adverse experience	1	0.01	1	0.01
Discontinued due to a vaccine-related adverse experience†	0	0.00	0	0.00
Discontinued due to a serious adverse experience	0	0.00	1	0.00
Discontinued due to serious vaccine-related adverse experience†	0	0.00	0	0.00
Adverse Event Monitoring Substudy	(N = 3345)		(N = 3271)	
Number of subjects	3345		3271	
Subjects with safety follow-up	3326	99.4	3249	99.3
Subjects without safety follow-up	19	0.6	22	0.7
Serious adverse experiences (SAEs)	**64**	**1.92**	**41**	**1.26**
Serious vaccine-related adverse experiences†	0	0.00	1	0.03
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	1	0.01
Discontinued due to serious vaccine-related adverse experience†	0	0.00	0	0.00

Adverse Event Monitoring Substudy by Age	Zoster Vaccine				Placebo			
	60-69 yrs		≥ 70 yrs		60-69 yrs		≥ 70 yrs	
Number of subjects	1732		1613		1727		1544	
Subjects with safety follow-up	1726		1600		1709		1540	
Subjects w/out safety follow-up	6		13		18		4	
	n	(%)	n	(%)	n	(%)	N	(%)
No adverse experience (AE)	605	35.05	792	49.50	1065	62.32	1067	69.29
One or more AE	1121	64.95	808	50.50	644	37.68	473	30.71
Injection-site AE	977	56.60	627	39.19	326	19.08	213	13.83
Systemic AE	451	26.13	369	23.06	430	25.16	338	21.95
Vaccine-related AE†	1006	58.29	660	41.25	375	21.94	265	17.21
Injection-site AE‡	977	56.60	625	39.06	325	19.02	211	13.70
Systemic AE	119	6.89	90	5.63	86	5.03	74	4.81
Serious AE (SAE)	**22**	**1.27**	**42**	**2.63**	**18**	**1.05**	**23**	**1.49**
Serious vaccine-related† AE	0	0.00	0	0.00	1	0.06	0	0.00
Died	1	0.06	2	0.13	1	0.06	1	0.06
Discontinued:								
Due to AE	0	0.00	0	0.00	0	0.00	0	0.00
Due to vaccine-related AE†	0	0.00	0	0.00	0	0.00	0	0.00
Due to serious AE	0	0.00	0	0.00	0	0.00	0	0.00
Due to serious vaccine-related AE†	0	0.00	0	0.00	0	0.00	0	0.00

‡All injection-site adverse experiences reported regardless of investigator assessment.
Subject w/≥ 1 safety follow-up Days 0-42 postvaccination - considered to have safety follow-up for the period.
N = Number of subjects vaccinated in AE Monitoring Substudy. n = Number of subjects in respective category

(Source: STN 125123, Protocol 004, Tables 8-1, 8-3, 11-123, 11-123)

Subjects in the AE Monitoring Substudy recorded episodes of erythema, swelling, and pain/tenderness on days 0-4 postvaccination using the Vaccine Report Card (VRC). The rates of AEs reported in the substudy are shown in Table 9-30.

Table 9-27 Injection-Site AEs Days 0-42 Postvaccination in AE Monitoring Substudy

	Zoster Vaccine (N = 3345)		Placebo (N = 3271)		Risk Difference Percentage Points (95% CI)‡	p-Value‡
	n	Risk† (%)	n	Risk† (%)		
Number of subjects	3345		3271			
With safety follow-up	3326		3249			
Without safety follow-up	19		22			
Number (%) of subjects w/ ≥1	1604	(48.3)	539	(16.6)		
Injection-site adverse experiences						
Erythema§	1188	(35.8)	227	(7.0)	28.8 (26.9, 30.6)	<0.001
Pain/Tenderness§	1147	(34.5)	278	(8.5)	26.0 (24.1, 27.9)	<0.001
Swelling§	871	(26.2)	147	(4.5)	21.7 (20.1, 23.4)	<0.001
Rash	10	(0.3)	3	(0.1)	0.2 (-0.0, 0.5)	0.058
Allergic reaction	1	(0.0)	0	(0.0)	0.0 (-0.1, 0.2)	N/A
Hematoma	53	(1.6)	46	(1.4)	0.2 (-0.4, 0.8)	N/A
Hypersensitivity	3	(0.1)	1	(0.0)	0.1 (-0.1, 0.2)	N/A
Hypoesthesia	1	(0.0)	0	(0.0)	0.0 (-0.1, 0.2)	N/A
Lesions	1	(0.0)	2	(0.1)	-0.0 (-0.2, 0.1)	N/A
Mass	30	(0.9)	2	(0.1)	0.8 (0.5, 1.2)	N/A
Myalgia	1	(0.0)	0	(0.0)	0.0 (-0.1, 0.2)	N/A
Other	22	(0.7)	10	(0.3)	0.4 (0.0, 0.7)	N/A
Paresthesia	4	(0.1)	2	(0.1)	0.1 (-0.1, 0.3)	N/A
Pruritus	237	(7.1)	33	(1.0)	6.1 (5.2, 7.1)	N/A
Rash, macular, papular	6	(0.2)	2	(0.1)	0.1 (-0.1, 0.3)	N/A
Rash, vesicular, bullae	4	(0.1)	1	(0.0)	0.1 (-0.1, 0.3)	N/A
Warmth	57	(1.7)	11	(0.3)	1.4 (0.9, 1.9)	N/A

†Risk in proportion: weighted average of risks stratified by age weighted by # subjects w/ follow-up in each age group.
‡Risk difference: Risk in zoster vaccine group - Risk in placebo group. CI & p-value computed by asymptotic method for difference of two binomial proportions. Risk differences & CIs provided for VRC queries & for events w/incidence rate ≥1% in at least one vaccination groups; p-values are provided only for events prompted for on the VRC.
§Vaccine report card (VRC) prompted only for these items.
AE Monitoring Substudy subjects used VRCs to record daily AEs, Days 0-42 postvaccination & contacted around Day 43 postvaccination to capture any additional AEs or cases of herpes zoster that were not already reported to study site.
Monthly telephone contacts made using ATRS to capture signs/symptoms of herpes zoster & any hospitalization.
If subject ≥ 2 adverse experiences in a category (e.g., multiple episodes of erythema), subject counted only once within that category. Same subject may appear in different adverse experience categories.
N = Number subjects vaccinated in AE Monitoring Substudy n = Number subjects in respective category.
N/A = Not Applicable CI = Confidence interval ATRS = Automated telephone response system.
AE terms from COSTART Version 2; conditions not in COSTART dictionary used term from Case Report Form.

(Source: STN 125123, Protocol 004, Table 8-5)

Solicited and unsolicited AEs were not reported separately.

Erythema, pain/tenderness and swelling were reported at higher rates in the overall zoster vaccine group than in placebo group. (p-values all < 0.001). These events were specifically queried by VRC. The other specific events listed in the injection-site AE table (above) were not.

Note that all injection-site adverse experiences were considered vaccine-related, regardless of investigator assessment. This would potentially impact the overall rate of vaccine-related events, since the vast majority of every other kind of AE were determined unrelated by the investigator.
The majority of injection-site experiences were reported resolved by Day 4.

Incidences of injection site erythema, pain/tenderness, and swelling were numerically greater among subjects in the younger age group (60 to 69 years old) compared with those in the older age group (70 years and older) and among female subjects compared with male subjects.

The most frequently reported non-solicited systemic clinical adverse experiences were headache, respiratory infection, and rash. (≥2% in at least one vaccination group)

Numerically, higher incidences of vaccine-related fever, diarrhea, headache, and maculopapular rash were observed in zoster vaccine recipients when compared with those receiving placebo. (all <1.5%)
No statistically significant differences between treatment groups were seen in the rate of these systemic clinical adverse experiences.

Serious Adverse Events
Within the AE Monitoring Substudy, rates of SAEs reported to occur within 42 days postvaccination were 1.92% in the ZOSTAVAX™ group and 1.26% in the placebo group. Subjects ≥ 70 years old enrolled in the AE Monitoring Substudy had a higher rate of SAES in the ZOSTAVAX™ group (2.63%) compared to the placebo group (1.49%). Small increases in the rate of SAEs in the ZOSTAVAX™ group as compared to the placebo group are also noted when the AE Monitoring Substudy treatment groups in both genders. A higher rate of SAEs occurring within 42 days postvaccination is not seen in the ZOSTAVAX™ group within the Routine Safety Monitoring Cohort. The clinical relevance of the observation is unclear.

Deaths Days 0-42 Postvaccination
A total of 30 deaths were reported as occurring between Days 0 and 42 postvaccination (14 in the zoster vaccine group, 16 in the placebo group). None of these deaths was determined to be related to the study vaccine by the reporting investigators. Narratives are not provided for deaths per se, but narratives of serious adverse experiences with onset dates between Days 0 and 42 postvaccination that led to death are provided.

It is difficult to draw conclusions from the deaths as reported as occurring Day 0-42 postvaccination (Table 9-44) as 26 of 30 deaths occurred in the Routine Monitoring Cohort which was more passively monitored. In addition, Day 42 safety follow-up included responses from only 55% of the entire study population (and additional data from 11.4% of study subjects, entered by investigators over 4+ years postvaccination).

Table 9-28 Serious Adverse Events Days 0-42 Postvaccination that Led to Death

Treatment	Gender	Race	Age (Yrs)	AE Substudy	Relative Day of Onset	Adverse Experience
ZOSTAVAX	M	White	76	No	9	Arteriosclerotic cardiovascular
						Hypertensive cardiovascular disease
ZOSTAVAX	M	White	77	No	10	Infarction, myocardial
ZOSTAVAX	M	White	62	No	12	Heart arrest; infarction, myocardial
ZOSTAVAX	M	White	64	No	13	Infarction, myocardial
ZOSTAVAX	M	White	75	Yes	20	Infarction, myocardial
ZOSTAVAX	M	White	68	No	20	Infarction, myocardial
ZOSTAVAX	M	White	65	Yes	22	Carcinoma, gastrointestinal
ZOSTAVAX	F	White	89	No	24	Cerebrovascular accident
ZOSTAVAX	F	White	76	No	24	Cerebrovascular accident
ZOSTAVAX	F	White	64	No	26	Infarction myocardial; heart arrest
ZOSTAVAX	M	White	78	No	26	Heart arrest; ischemia, myocardial
ZOSTAVAX	M	White	69	No	36	Cardiovascular disorder
ZOSTAVAX	F	White	64	No	37	Carcinoma, gastrointestinal
ZOSTAVAX	M	White	77	Yes	43	Heart failure, right
Placebo	M	White	72	No	6	Heart arrest
Placebo	F	White	70	No	7	Infarction, myocardial
Placebo	M	White	68	No	14	Carcinoma
Placebo	F	Black	62	No	15	Convulsions; heart arrest; infarction, myocardial
Placebo	M	White	67	No	16	Pneumonia, aspiration
					20	Heart arrest; heart failure
Placebo	M	White	67	Yes	17	Heart failure; infarction, myocardial
Placebo	M	White	79	No	18	Infarction, myocardial
Placebo	M	White	74	No	20	Cerebrovascular accident
Placebo	F	White	62	No	21	Carcinoma, lung
Placebo	M	White	71	No	22	Carcinoma, lung
Placebo	M	White	78	No	28	Apnea; heart arrest; infarction, myocardial; intestinal obstruction; pneumonia; sepsis
Placebo	M	White	75	Yes	29	Carcinoma, lung
Placebo	M	White	78	No	31	Death, sudden
Placebo	M	White	64	No	38	Gangrene, intestinal
Placebo	M	White	67	No	38	Liver failure
Placebo	M	White	71	No	42	Heart arrest

AN=Allocation Number; This table created from clinical database counting date of vaccination = Day 1. Relative days of onset in this table appear to be one day later than actual days of onset. AE terms from COSTART Version 2. Conditions not captured by COSTART were assigned a term from Case Report Form

(Source STN 125123, Protocol 004, Tables 11-145 thru 11-172)

Safety Data from Day 42 Through End of Study

Automated Telephone Response System (ATRS)

No information has been submitted to the BLA regarding the proportion of subjects with contact at each month overall and, by site. This makes it difficult to interpret the submitted safety data. It should be noted that such data were to be submitted to the DSMB for review.

Table 9-32 shows the number of subjects with safety follow-up from Day 43 postvaccination to the end of the study. Discontinuations are also indicated. As noted earlier in this document, safety data after Day 42 was passively collected. Site personnel were also to review medical records to capture relevant AEs.

Table 9-29 Clinical AEs, Day 43 Postvaccination to End of Study

Routine Safety Monitoring Cohort				
	Zoster Vaccine		Placebo	
	n	(%)	n	(%)
Number of subjects	15925		16005	
Subjects with safety follow-up	15915		15992	
Subjects without safety follow-up	10		13	
Number (%) of subjects				
with serious vaccine-related adverse experiences (AEs)†	0	(0.00)	1	(0.01)
discontinued due to an AE	7	(0.04)	13	(0.08)
discontinued due to a vaccine-related† AE	0	(0.00)	0	(0.00)
discontinued due to a serious AE	7	(0.04)	12	(0.08)
discontinued due to a serious vaccine-related AE†	0	(0.00)	0	(0.00)
Adverse Event Monitoring Substudy				
	Zoster Vaccine (N = 3345)		Placebo (N = 3271)	
	n	(%)	n	(%)
Number of subjects	3345		3271	
Subjects with safety follow-up	3342		3268	
Subjects without safety follow-up	3		3	
Number (%) of subjects				
with serious vaccine-related AE†	0	(0.00)	0	(0.00)
discontinued due to an adverse experience	3	(0.09)	4	(0.12)
discontinued due to a vaccine-related AE†	0	(0.00)	0	(0.00)
discontinued due to a serious adverse experience	3	(0.09)	4	(0.12)
discontinued due to a serious vaccine-related AE†	0	(0.00)	0	(0.00)

†Determined by investigator as possibly, probably, or definitely related to the vaccine.
Routine Safety Monitoring Cohort: Subjects to report AEs occurring Days 0 to 42 postvaccination directly to study site staff, by telephone or visit.
Adverse Event Monitoring Substudy: Subjects provided Vaccination Report Cards to record daily AEs occurring Days 0-42 postvaccination.
All Subjects: Contacted around Day 43 postvaccination to capture AEs or HZ not already reported.
ATRS conducted monthly telephone follow-up to capture signs/symptoms of HZ.
Subject w/ $\geq$ 1 safety follow-up contact Days 0-42 is considered to have safety follow-up for the period.
N = Number of subjects vaccinated in the Routine Safety Monitoring Cohort.
n = Number of subjects in the respective category. ATRS = Automated telephone response system.

(Source: STN 125123, Protocol 004, Tables 8-2, 8-4)

Table 9-30 AEs Day 43 Postvaccination to Study End – AE Monitoring Substudy (Incidence > 0%)

	Zoster Vaccine	Placebo
	n	N
Adverse Event Monitoring Substudy		
Number of subjects	3345	3271
Subjects with safety follow-up	3342	3268
Subjects without safety follow-up	3	3
Number of subjects w/ ≥1 systemic adverse experiences	1195	1194
Cardiovascular	369	377
Digestive	213	179
Endocrine	9	15
General body	319	344
Genitourinary	168	184
Hemic & lymphatic	25	26
Metabolic/nutritional	32	41
Musculoskeletal	222	230
Nervous system	150	154
Respiratory	144	161
Sight/sense	9	13
Skin	106	102
Surgical, medical and diagnostic	5	1
Routine Safety Monitoring Cohort		
Number of subjects	15925	16005
Subjects with safety follow-up	15915	15992
Subjects without safety follow-up	10	13
Number of subjects with one or more systemic adverse experiences	371	406
Cardiovascular	32	26
Digestive	15	13
Endocrine	0	2
General body	45	49
Genitourinary	5	11
Hemic & lymphatic	7	6
Metabolic/nutritional	2	3
Musculoskeletal	8	20
Nervous system	16	25
Respiratory	19	15
Sight/sense	4	5
Skin	248	260

†Term from COSTART Version 2; no inference can be made regarding evaluable status (hierarchical algorithm).
Adverse Event Monitoring Substudy: Used VRCs to record daily AEs occurring Days 0-42 postvaccination.
Subjects contacted around Day 43 postvaccination to capture additional AEs or HZ not already reported.
Routine Safety Monitoring Cohort: To report AEs occurring Days 0-42 postvaccination directly to study site staff, by telephone or visit.
All subjects: Monthly ATRS follow-up to capture suspected herpes zoster (hospitalization in AE monitoring substudy).
Percentages are calculated based on the number of subjects with follow-up.
Subjects w/ contacts after Day 42 postvaccination considered to have follow-up Day 43 – study end.
If a subject had 2 or more adverse experiences, the subject is counted only once in the overall total.
All body systems are listed in which at least 1 subject had an adverse experience.
N = Number of subjects in AE Monitoring Substudy. n = Number of subjects in respective category.
ATRS = Automated telephone response system. AE terms are from COSTART Version
Conditions not captured by COSTART were assigned a corresponding term from the Case Report Form.

(Source: STN 125123, Protocol 004, pages 2664 - 2676)

Adverse Events following contact at or around Day 42 were not routinely monitored or collected. Events that subjects did report were summarized.

With the exception of headache, no statistically significant differences were observed between the two vaccination groups with respect to any reported vaccine-related systemic clinical adverse experiences in the AE Monitoring Substudy in the period from Day 43 to end of study.

A subject who had contact after Day 42 postvaccination is considered to have follow-up for the period from Day 43 postvaccination through the end of study. This would appear to include the contact at or around Day 42, so that subjects with essentially no safety follow-up after the period on or around Day 42 would be counted as having safety follow-up to the end of the study which was planned to last for ~4.5 years postvaccination.

Table 9-31 Summary of Deaths During the Entire Study Among All Study Participants

Age Group (years)	Zoster Vaccine (N=19270)			Placebo (N=19276)		
	Observed Proportion n/m (%)	Total Follow-Up Time† (Person-Years)	Observed Rate of Death per 1000-Person Years (95% CI)	Observed Proportion n/m (%)	Total Follow-Up Time† (Person-Years)	Observed Rate of Death per 1000-Person Years (95% CI)
60 to 69	218/10378 (2.10)	35162.2	6.20 (5.40, 7.08)	246/10369 (2.37)	35161.8	7.00 (6.15, 7.93)
≥70	575/8892 (6.47)	30139.6	19.08 (17.55, 20.70)	549/8907 (6.16)	30292.7	18.12 (16.64, 19.70)
All	793/19270 (4.12)	65301.8	12.14 (11.31, 13.02)	795/19276 (4.12)	65454.6	12.15 (11.32, 13.02)

†For a subject who died during the study, the follow-up time is the number of days from vaccination to the date of death; if the date of death is unknown, the follow-up time is the number
of days from vaccination to the last day of study follow-up.
N = Number of subjects vaccinated in the study.
n = Number of subjects in the respective age group who died during the study.
m = Number of subjects in the respective age group who had follow-up information with respect to death.
CI = Confidence interval.

(Source: STN 125123, Protocol 004, Table 8-12)

Similar death rates were also observed in the 2 vaccination groups when analyzed by age strata, gender and race group.

Tertiary Endpoint: Evaluation of Potential Covariates on HZ Pain BOI and Vaccine Efficacy

The study report contained an evaluation of the following potential covariates: treatment, gender, age, use of antiviral drugs and use of analgesic drugs. Age was shown to significantly and consistently affect HZ BOI pain severity-by-duration scores, incidence of PHN and incidence of HZ, while medication use and gender did not.

Table 9-32 Effect of Covariates (Including Analgesic Drug) on Severity-by-Duration Scores of HZ Pain Among Evaluable HZ Cases (MITT Population)

Parameter	Estimate	Standard Error	p-Value†
Treatment (Vaccine vs. Placebo)	-35.065	13.909	0.012
Gender (Female vs. Male)	-19.691	13.967	0.159
Subject age (Years)	4.665	1.092	<0.001
Use of Antiviral Drug During 6-Month HZ Follow-up (Yes vs. No)	30.915	20.822	0.138
Use of Analgesic During 6-Month HZ Follow-up (Yes vs. No) ‡	161.626	16.744	<0.001

p-Value for testing treatment-by-gender interaction was 0.143
p-Value for testing treatment-by-age interaction was 0.031
p-Value for testing treatment-by-antiviral-drug-use interaction was 0.381
p-Value for testing treatment-by-analgesic-drug-use interaction 0.293.
†Computed based on an analysis of covariance (ANCOVA) model that included severity-by-duration score of HZ pain as the response variable, and vaccination group, gender, age, use of analgesic, and antiviral drug as explanatory variables.
‡Analgesic use included subjects who used acetaminophen, non-steroidal anti-inflammatories, opiates, and topical anesthetics.
MITT population: All randomized subjects who were followed ≥ 30 days postvaccination and did not develop evaluable cases of HZ (per the hierarchical algorithm specified in Protocol Amendment 6) within the first 30 days postvaccination.
HZ = Herpes zoster MITT = Modified intention-to-treat

(Source: STN 125123, Protocol 004 Table 11-74)

Table 9-33 Analysis of Effect of Covariates on the Severity-by-Duration Scores (MITT Population)

Parameter	Estimate	Standard Error	p-Value†
Treatment (Vaccine vs. Placebo)	-39.046	14.717	0.008
Gender (Female vs. Male)	-16.008	14.763	0.278
Subject age (Years)	5.270	1.154	<0.001
Antiviral drug initiated w/in 72 hrs of rash onset (Yes vs. No)	12.929	15.269	0.397

p-Value for testing treatment-by-gender interaction was 0.222
p-value for testing treatment-by-age interaction was 0.073
p-value for testing treatment-by-antiviral-drug-use interaction was 0.371.
†Computed based on an analysis of covariance (ANCOVA) model that included severity-by-duration score of HZ pain as the response variable, and vaccination group, gender, age, and use of antiviral drug as explanatory variables.
The MITT population included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop evaluable cases of HZ (per the hierarchical algorithm specified in Protocol Amendment 6) within the first 30 days postvaccination.
HZ = Herpes zoster. MITT = Modified intention-to-treat.

(Source: STN 125123, Protocol 004 Table 7-40)

Table 9-34 Statistical Analysis of Effect of Covariates on the Incidence of PHN (MITT Population)

Parameter		Regression Coefficient	Std. Error	Estimated Relative Risk of PHN (95% CI)	p-Value†
Treatment	Vaccine vs. Placebo	-0.484	0.209	0.616 (0.409, 0.928)	0.021
Gender	Female vs. Male	-0.360	0.189	0.697 (0.482, 1.009)	0.056
Subject Age	Years	0.066	0.013	1.068 (1.041, 1.096)	<0.001
Antiviral Drug w/in 72 hours of rash onset	Yes vs. No	0.163	0.197	1.177 (0.800, 1.732)	0.408

p-Value for testing treatment-by-gender interaction was 0.751;
p-value for testing treatment-by-age interaction was 0.886;
p-value for testing treatment-by-antiviral-drug-use interaction was 0.488.
†Computed based on a logistic regression model that included PHN case indicator as the response variable, and vaccination group, gender, age, and use of antiviral drug as explanatory variables.
MITT: All randomized subjects who were followed ≥30 days postvaccination and did not develop evaluable cases of HZ (per the hierarchical algorithm, Protocol Amendment 6) within the first 30 days postvaccination.
HZ = Herpes zoster. PHN = Postherpetic neuralgia.
MITT = Modified intention-to-treat. CI = Confidence interval.

(Source: STN 125123, Protocol 004, Table 7-39)

The use of antiviral therapy for the treatment of HZ did not have a statistically significant effect on the incidence of PHN or the severity-by-duration of HZ pain among evaluable HZ cases.

Table 9-35 Summary of Antiviral Use Initiated Within 72 Hours of Rash Onset (MITT)

Age Group (years)	Zoster Vaccine (N=19270)		Placebo (N=19276)	
	% (s/n)	95% CI	% (s/n)	95% CI
60 to 69	59.84 (73/ 122)	(50.58, 68.61)	66.47 (222/ 334)	(61.13, 71.51)
≥70	66.84 (129/ 193)	(59.72, 73.43)	65.26 (201/ 308)	(59.65, 70.57)
All	64.13 (202/ 315)	(58.56, 69.43)	65.89 (423/ 642)	(62.08, 69.55)

The MITT population included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop evaluable cases of HZ (per the hierarchical algorithm specified in the Protocol Amendment 6) within the first 30 days postvaccination.
N = Number of subjects randomized.
n = Number of evaluable HZ cases.
s = Number of subjects who initiated use of antiviral drugs w/in 72 hours of HZ rash onset.
HZ = Herpes zoster. MITT = Modified intention-to-treat. CI = Confidence interval.

(Source: STN 125123, Protocol 004, Table 7-38)

Table 9-36 Antiviral and Analgesic Drug Use During 6 Month HZ Follow-Up Evaluable HZ Cases or PHN Cases (MITT Population)

Endpoint	Drug Used During 6-Month of HZ Follow-Up	Zoster Vaccine		Placebo	
		n	%	n	%
Evaluable HZ Cases	Antiviral	275	87.3	550	85.7
	Analgesic†	236	74.9	496	77.3
PHN Cases	Antiviral	27	100.0	75	93.8
	Analgesic†	27	100.0	80	100.0

†Analgesics: acetaminophen, non-steroidal anti-inflammatories, opiates, topical anesthetics
MITT: All randomized subjects who were followed ≥ 30 days postvaccination and did not develop evaluable cases of HZ (hierarchical algorithm, Protocol Amendment 6) w/in first 30 days postvaccination.
MITT = Modified intention-to-treat. HZ = Herpes zoster. PHN = Postherpetic neuralgia.

(Source: STN125123, Protocol 004, Table 7-41)

9.5 Other Prespecified Efficacy Analysis

(Not listed as study objective or endpoints in the Protocol Synopsis or Protocol 004 Clinical Study Report)
In subjects who developed HZ subsequent to vaccination, zoster vaccine reduced the HZ pain severity-by-duration compared with placebo (mean severity-by-duration score among HZ cases in the zoster vaccine group and the placebo group: 141.2 vs. 180.5; p-value = 0.008 among evaluable HZ cases).

10 PROTOCOL 009

Title: 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

10.1 Objective

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).

10.2 Design

Protocol 009 is a randomized, double-blind, placebo-controlled, 18-center study comparing the safety profile of a higher potency zoster vaccine (~207,000 PFU/0.65-mL dose) with that of a lower potency (~58,000 PFU/0.65-mL dose) that had been assessed in prior clinical studies.

Subjects were followed for local and systemic clinical adverse experiences, varicella or varicella-like rash, and herpes zoster (HZ) or HZ-like rash for 42 days postvaccination.

10.3 Population

The study planned enrollment of approximately 700 adults, 50 years of age and older, stratified by age (50-59 years, ≥ 60 years of age).

10.4 Enrollment Criteria

- Healthy
- Varicella history-positive
- HZ history-negative
- Male or female subjects ≥ 50 years of age
- Females postmenopausal or with a negative urine 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 given within 5 months prior to or expected during 42 days after vaccination
- No live vaccinations within 6 weeks prior and until 42 days after vaccination
- No inactivated vaccinations within 7 days prior to and until 42 days 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, no participation in an investigational study within 30 days prior to vaccination.

10.5 Vaccine Administration / Dose Selection

2 different potencies of ZOSTAVAX™ were administered:
Higher potency vaccine (~207,000 PFU/0.65 mL)
Lower potency vaccine (~58,000 PFU/0.65 mL).

The lower potency dose is similar to the highest doses administered in Protocol 004.

For administration, both the higher and lower potency vaccines were reconstituted with 0.7 mL of sterile diluent. In order to administer the higher potency formulation in an acceptable volume, the higher potency

vaccine was manufactured by an overfill strategy, i.e., prior to lyophilization, vaccine vials were filled with 1.0 mL of the
vaccine formulation, rather than the standard volume of 0.7 mL. Therefore, the osmolality, component concentrations (e.g., gelatin, salts, sucrose) and cell cultured residuals of the higher potency vaccine were approximately 1.43 times those of VARIVAX™ and also of the lower potency vaccine in this study.
The sterile diluent provided was 0.7 mL of sterile water without preservatives, supplied in glass vials and could have been either refrigerated at 2 to 8° C or stored at room temperature, per protocol.

Table 10-1 Number of Subjects by Age and Treatment Group

Vaccine Groups	50-59 Years	≥60 Years	Total
Higher potency dose	123	341	464
Lower potency dose	62	172	234
Total	185	513	698

(Source: STN 125123, Protocol 009 Table 6-3)

10.6 Endpoints

- Vaccine-related serious clinical adverse experiences occurring Day 1 through Day 42 postvaccination
- Composite endpoint 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 to historical PNEUMOVAX™23 control.

Statistical Considerations
The probability of observing at least one serious clinical adverse experience depends on the number of subjects enrolled and the incidence rate of serious clinical adverse experiences in the general population. If the incidence rate of a serious clinical adverse experience was 0.47%, then there was an 85% chance of observing at least one such serious adverse experience.

A test of risk difference between treatment groups, performed at the 2-sided 0.05 level would provide 97.5% confidence that the true rate was < 0.92% with ~ 400 subjects in higher potency vaccine group and ~ 200 subjects in the lower potency vaccine group, if no serious clinical adverse experiences were observed in both groups.

The study had ~85% power to detect a 7.4-percentage-point increase in adverse event incidence rates in the higher potency vaccine group from a hypothetical incidence rate in the lower potency vaccine group of 5.0%.

Clinical significance for this endpoint was defined by the upper bound of the 95% confidence interval (CI) for the observed incidence rate exceeding 21.5%, which was pre-established based on past clinical trial experience with PNEUMOVAX™23 (pneumococcal vaccine polyvalent).

10.7 Evaluation / Follow-Up

There were no blood sampling or immunogenicity evaluations.

Safety Follow-Up
42-Day Diary Cards were used to capture oral temperatures, injection-site AEs, and systemic clinical AEs.

10.8 Results

Table 10-2 Subjects with Moderate-Severe Injection-Site Reactions, Day 1-5 Postvaccination

Parameter	Zoster Vaccine Higher Potency (N=461)		Zoster Vaccine Lower Potency (N=234)		Difference in Percentage (Higher - Lower Potency) (95% CI)
	n	% (95% CI)	N	% (95% CI)	
Number of subjects Subjects without follow-up Subjects with follow-up	461 2 459		234 0 234		
Subjects with moderate or severe injection-site pain/tenderness/soreness or swelling (> 2 inches at the largest diameter)	79	17.2 (13.9, 21.0)	21	9.0 (5.6, 13.4)	8.2 (2.9, 13.1)
† The upper bound of the 95% CI of incidence rate in the higher potency vaccine group was below the clinically meaningful limit (21.5%) that was pre-established based on the historical experience with PNEUMOVAX™23. Adverse experience terms are from MedDRA Version 7.0. N = Number of subjects vaccinated in each group. n = Number of subjects in each category. CI = Confidence Interval.					

(Source: STN 125123, Protocol 009 Table 8-9)

Rates of systemic and vaccine-related systemic AEs were similar between treatment groups as shown in the following tables.

The high-potency vaccine group experienced higher rates of solicited AEs (pain, tenderness, soreness and swelling) and, higher rates of non-solicited AEs (pruritus, swelling and warmth). There were no severe local injection-site reactions.

There were few systemic AEs rated as severe. In the lower potency group no more than 1 subject reported any specific severe AE. In the higher potency group there were 6 subjects with severe headache, 2 subjects with severe arthralgias, 3 with severe upper respiratory infection and 2 with severe nasopharyngitis.

Incidence of temperature > 101ºF was < 1% in both treatment groups

Table 10-3 AEs Reported Days 0-42 Postvaccination

	Zoster Vaccine Higher Potency (N=461)		Zoster Vaccine Lower Potency (N=234)	
	N	(%)	n	(%)
Number of subjects	461		234	
Subjects without follow-up	2		0	
Subjects with follow-up	459		234	
Number (%) of subjects:				
No adverse experience (AE)	121	(26.4)	66	(28.2)
One or more AEs	338	(73.6)	168	(71.8)
Injection-site AEs	289	(63.0)	140	(59.8)
Systemic AEs	172	(37.5)	92	(39.3)
Vaccine-related† AE	300	(65.4)	145	(62.0)
Injection-site AE	289	(63.0)	140	(59.8)
Systemic AE	50	(10.9)	31	(13.2)

Serious adverse experiences (SAE)	4	(0.9)	1	(0.4)
Serious vaccine-related AE	0	(0.0)	0	(0.0)
Died	0	(0.0)	0	(0.0)
Discontinued‡ due to AE	0	(0.0)	0	(0.0)
discontinued due to a vaccine-related AE	0	(0.0)	0	(0.0)
discontinued due to SAE	0	(0.0)	0	(0.0)
discontinued due to SAE vaccine-related AE	0	(0.0)	0	(0.0)

† Determined possibly, probably, or definitely related to vaccine by investigator.
‡ Discontinued = Subject discontinued from study.
Percentages calculated based on number of subjects with follow-up after vaccination.
N= Number of subjects vaccinated in each group.
n= Number of subjects in each group.

(Source: STN 125123, Protocol 009, Table 8-1)

Table 10-4 Injection-Site Adverse Experiences (Days 1 to 5 Postvaccination)

	ZOSTAVAX™ Higher Potency		ZOSTAVAX™ Lower Potency	
	(N=461)		(N=234)	
	AE		AE	
	n	(%)	n	(%)
Number of subjects	461		234	
Without follow-up	2		0	
Subjects with follow-up	459		234	
≥ 1 injection-site AE	286	(62.3)	140	(59.8)
Injection-Site Bruising	6	(1.3)	4	(1.7)
Injection-Site Desquamation	1	(0.2)	0	(0.0)
Injection-Site Discomfort	0	(0.0)	1	(0.4)
Injection-Site Erythema	225	(49.0)	111	(47.4)
Injection-Site Induration	4	(0.9)	1	(0.4)
Injection-Site Nodule	1	(0.2)	0	(0.0)
Injection-Site Pain	216	(47.1)	91	(38.9)
Injection-Site Pruritus	57	(12.4)	19	(8.1)
Injection-Site Pustule	0	(0.0)	1	(0.4)
Injection-Site Rash	4	(0.9)	0	(0.0)
Injection-Site Reaction	1	(0.2)	0	(0.0)
Injection-Site Swelling	188	(41.0)	77	(32.9)
Injection-Site Warmth	18	(3.9)	6	(2.6)

Vaccination report card (VRC) prompted subject to record swelling, erythema and pain/tenderness/soreness; pain/tenderness/soreness mapped to injection-site pain in the clinical database.
Percentages calculated based on number of subjects with follow-up after vaccination.
Subject may have had ≥ 2 adverse experiences, but is counted only once in overall total.
AE terms from MedDRA Version 7.0. N = # subjects vaccinated in group.
n = # subjects in each category.

(Source: STN 125123, Protocol 009 Table 8-4)

Table 10-5 shows the rates of injection-site AEs reported to occur within 5 days postvaccination with high and low potency ZOSTAVAX™ in the 50-59 year old and ≥ 60 year old cohorts.

Table 10-5 Analysis of Injection-Site AEs in Subjects 50-59 Years of Age (Days 1-5 Postvaccination)

Number of subjects	Zoster Vaccine Higher Potency (N=123)		Zoster Vaccine Lower Potency (N=62)		Difference in Percentage [Higher - Lower Potency] (95% CI)†	p-Value
Subjects 50-59 years old						
	n	(%)	n	(%)		
Subjects w/out follow-up	0		0			
Subjects with follow-up	123		62			
Subjects with ≥ 1 injection-site AE	102	(82.9)	43	(69.4)		
adverse experiences						
Injection-Site Bruising	3	(2.4)	0	(0.0)	2.4 (-3.5,6.9)	N/A
Injection-Site Discomfort	0	(0.0)	1	(1.6)	-1.6 (-8.6,1.5)	N/A
Injection-Site Erythema	83	(67.5)	35	(56.5)	11.0 (-3.6,25.8)	0.142
Injection-Site Pain	84	(68.3)	32	(51.6)	16.7 (1.8,31.3)	0.027
Injection-Site Pruritus	25	(20.3)	4	(6.5)	13.9 (3.2,23.1)	N/A
Injection-Site Pustule	0	(0.0)	1	(1.6)	-1.6 (-8.6,1.5)	N/A
Injection-Site Swelling	73	(59.3)	27	(43.5)	15.8 (0.5,30.4)	0.042
Injection-Site Warmth	8	(6.5)	1	(1.6)	4.9 (-2.6,11.0)	N/A
Subjects ≥ 60 years old						
	n	(%)	n	(%)		
Number of subjects	338		172			
Subjects w/out follow-up	2		0			
Subjects with follow-up	336		172			
Subjects w/ ≥ 1 injection-site AE	184	(54.8)	97	(56.4)		
Injection-Site Bruising	3	(0.9)	4	(2.3)	-1.4 (-5.0,0.7)	N/A
Injection-Site Erythema	142	(42.3)	76	(44.2)	-1.9 (-11.1,7.1)	0.679
Injection-Site Pain	132	(39.3)	59	(34.3)	5.0 (-4.0,13.6)	0.273
Injection-Site Pruritus	32	(9.5)	15	(8.7)	0.8 (-5.0,5.8)	N/A
Injection-Site Rash	4	(1.2)	0	(0.0)	1.2 (-1.0,3.0)	N/A
Injection-Site Swelling	115	(34.2)	50	(29.1)	5.2 (-3.5,13.4)	0.241
Injection-Site Warmth	10	(3.0)	5	(2.9)	0.1 (-3.9,3.0)	N/A

† Risk differences and CIs provided for events prompted on Vaccination Report Card (VRC) and for events with incidence rate ≥1% in one or more groups.
P-values are provided only for events prompted for on the VRC.
CI on risk difference and p-value for testing of risk difference are computed based on an asymptotic method for the difference of 2 binomial proportions.
VRC prompted subject to record injection-site pain/tenderness/soreness; mapped to pain in clinical database.
Although a subject may have had 2 or more adverse experiences in an adverse experience category (i.e., multiple episodes of erythema), the subject is counted only once within that category. The same subject may appear in different adverse experience categories.
Adverse experience terms are from MedDRA Version 7.0.
N = # subjects vaccinated. n = # subjects with adverse experiences in the respective category.
N/A = Not applicable. CI = Confidence interval.

(Source: STN 125123, Protocol 009 Table 8-10, 8-11)

Table 10-6 Systemic AEs (Incidence ≥1%) by System Organ Class (Days 1-42 Postvaccination)

	ZOSTAVAX™ Higher Potency (N=461)		ZOSTAVAX™ Lower Potency (N=234)	
	AEs		AE	
	n	(%)	n	(%)
Number of subjects	461		234	
Subjects w/out follow-up	2		0	
Subjects with follow-up	459		234	
Subjects with ≥ 1 systemic AE	172	(37.5)	92	(39.3)
Subjects with no systemic AE	287	(62.5)	142	(60.7)
Ear And Labyrinth Disorders	4	(0.9)	4	(1.7)
Vertigo	1	(0.2)	3	(1.3)
Gastrointestinal Disorders	29	(6.3)	5	(2.1)
Diarrhea	11	(2.4)	2	(0.9)
Nausea	6	(1.3)	0	(0.0)
General Disorders & Administration Site	23	(5.0)	17	(7.3)
Conditions				
Fatigue	8	(1.7)	5	(2.1)
Pain	4	(0.9)	7	(3.0)
Pyrexia	6	(1.3)	3	(1.3)
Immune System Disorders	5	(1.1)	1	(0.4)
Infections And Infestations	48	(10.5)	27	(11.5)
Bronchitis	1	(0.2)	3	(1.3)
Nasopharyngitis	10	(2.2)	7	(3.0)
Sinusitis	6	(1.3)	2	(0.9)
Upper respiratory tract infection	10	(2.2)	8	(3.4)
Injury, Poisoning And Procedural Complications	10	(2.2)	2	(0.9)
Musculoskeletal, Connective Tissue Disorders	39	(8.5)	23	(9.8)
Arthralgia	8	(1.7)	3	(1.3)
Back pain	12	(2.6)	8	(3.4)
Myalgia	6	(1.3)	3	(1.3)
Pain in extremity	8	(1.7)	3	(1.3)
Nervous System Disorders	50	(10.9)	20	(8.5)
Headache	43	(9.4)	16	(6.8)
Psychiatric Disorders	7	(1.5)	1	(0.4)
Respiratory, Thoracic And Mediastinal Disorders	17	(3.7)	12	(5.1)
Cough	4	(0.9)	3	(1.3)
Pharyngolaryngeal pain	9	(2.0)	4	(1.7)
Skin And Subcutaneous Tissue Disorders	25	(5.4)	20	(8.5)
Dermatitis contact	1	(0.2)	3	(1.3)
Pruritus	9	(2.0)	2	(0.9)
Rash vesicular	2	(0.4)	4	(1.7)

(Source: STN 125123, Protocol 009 Table 8-12)

No varicella-like rashes with > 100 lesions were reported. 3 HZ-like rashes were reported in each treatment group. PCR results did not detect any case of Oka/Merck virus from varicella- or HZ-like rashes.

Serious Adverse Events and Deaths

5 SAEs occurred during the study, 1 in the lower potency ZOSTAVAX™ group and 4 in the higher potency ZOSTAVAX™ group. No deaths were reported.

Table 10-7 Subjects With Serious Clinical Adverse Experiences

Gender	Race	Age (Yrs)	Day of Onset	Adverse Experience	Intensity	Outcome
Zoster Vaccine Higher Potency						
Female	White	54	29	Depression	moderate	Recovered
Male	White	61	25	Angina pectoris	severe	recovered
Female	White	56	41	Enteritis	severe	recovered
Female	Black	66	13	Coronary artery disease	moderate	not recovered
Zoster Vaccine Lower Potency						
Male	White	58	3	Lung cancer	severe	not recovered

(Source: STN 125123, Protocol 009 Table 8-23)

These study results are considered descriptive. They serve to evaluate possible dose response relationship of solicited and adverse events in general over the selected dose range.

It is difficult to directly compare Protocol 0009 data to Protocol 004 data as the age ranges and stratification differ.

In general, younger subjects (50-59 year old) in Protocol 009 had higher rates of vaccine-related adverse events, and this difference is more pronounced in the higher potency group, e.g., 83% of those aged 50-59 had at least one injection-site AE, while only 55% of those aged ≥ 60 years and older experienced at least 1 injection-site AE.

No subjects died or discontinued from the study

5 Serious Adverse Events reported - four subjects in the higher potency vaccine group (0.9%) and one in the lower potency vaccine group (0.4%) reported serious clinical adverse events.

The useful of a 21.5% upper limit on the difference between proportion of subjects in the high vs. low potency ZOSTAVAX™ groups with moderate or severe injection-site pain, tenderness, soreness or swelling (>2 inches) based upon historical experience with PNEUMOVAX™23 is unclear.

A trend of increased SAEs in the Day 0-42 postvaccination period was also seen in Protocol 004 in the AE Monitoring Substudy. This increase was most notable in the ≥ 70 year old cohort in Protocol 004. The clinical relevance of these observations is not clear.

11.0 ADDITIONAL DATA TABLES FOR PROTOCOL 004

Additional Protocol 004 Demographic Data

Table 11-1 Enrollment by Gender

	Zoster Vaccine		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Protocol 004 (Overall)						
Male	11403	59.2	11357	58.9	22760	59.0
Female	7867	40.8	7919	41.1	15786	41.0
CMI Substudy						
Male	348	50.4	426	60.5	774	55.5
Female	343	49.6	278	39.5	621	44.5
AE Monitoring Substudy						
Male	1830	54.7	1847	56.5	3677	55.6
Female	1515	45.3	1424	43.5	2939	44.4

(Source: STN 125123; Protocol 004 Tables 6-12, 11-8, 11-9)

Table 11-2 Enrollment by Race

	Zoster Vaccine		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Protocol 004 (overall)						
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
CMI Substudy						
Black	1	0.1	6	0.9	7	0.5
Hispanic	6	0.9	11	1.6	17	1.2
White	676	97.8	679	96.4	1355	97.1
Other	8	1.2	8	1.1	16	1.1
AE Monitoring Substudy						
Black	58	1.7	68	2.1	126	1.9
Hispanic	43	1.3	36	1.1	79	1.2
White	3208	95.9	3131	95.7	6339	95.8
Other	36	1.1	35	1.1	71	1.1
Unknown	0	0.0	1	0.0	1	0.0

(Source: STN 125123; 5.3.5.1.1.4 Table 6-12, 11-8, 11-9)

Additional Protocol 004 Efficacy Data

Table 11-3 Subjects Included and Excluded in the Sensitivity Analyses of Vaccine Efficacy (MITT Population Excluding Major Protocol Deviations and Immunosuppressed Subjects)

	Zoster Vaccine (N = 19270)	Placebo (N = 19276)
Description	n	n
Subjects included in the MITT Population	19254	19247
Subjects included in the sensitivity analyses of the MITT population excluding protocol deviators	18967	18961
Subjects excluded from the sensitivity analyses of the MITT population excluding protocol deviators	287	286
Protocol Deviations in Eligibility Criteria		
Received immunosuppressive therapy	3	4
Had active neoplastic disease	2	1
Had history of herpes zoster†	1	1
Had prior receipt of varicella vaccine	1	2
Other Deviations Occurring After Enrollment During Follow-up		
Received 2 dose of blinded study vaccine	0	1
Prematurely unblinded to vaccination group	0	2
Received vaccine compromised by freezer temperature deviations‡	280	275
Subjects included in the sensitivity analyses of the MITT population excluding immunosuppressed subjects	18882	18869
Subjects excluded from the sensitivity analyses of the MITT population excluding immunosuppressed subjects§	372	378
Immunosuppressed at study entry	3	4
Immunosuppressed at onset of suspected HZ	24	23
Immunosuppressed at study termination	355	362

†One subject in the placebo group (AN 6301320) had a history of herpes zoster (developed HZ [per CEC adjudication] 2 days before vaccination) and was not included the MITT population.
‡ 557 subjects were included in the MITT analyses but excluded from sensitivity analyses based upon treatment received, as they were found to have received vaccine which had been stored in a freezer that experienced excursions above the recommended storage temperature. One additional subject (AN 6730292) in the placebo group and one additional subject (AN 6730950) in the zoster vaccine group who received vaccines compromised by freezer temperature deviations were discontinued within 30 days after vaccination. These 2 subjects were not included in the MITT population.
§A subject can be counted in more than 1 category
n = Number of subjects in the respective category
HZ = Herpes zoster
MITT = Modified intention-to-treat
N = Number of subjects randomized
AN = Allocation number
CEC = Clinical Evaluation Committee

(Source: (STN 125123; Protocol 004 Table 11-3)

.

Table 11-4 Severity-by-Duration Scores of HZ Pain by Time After Rash Onset (Evaluable HZ Cases – MITT) - Tertiary Analysis

Days after Rash Onset	Age Group (Years)	Zoster Vaccine (N = 19270)					Placebo (N = 19276)				
		n	Range (Min. - Max.)	SD	Median	Mean (95% CI)	n	Range (Min. - Max.)	SD	Median	Mean (95% CI)
0-30	60 to 69	122	0.0 to 287.4	66.3	69.8	84.4 (72.5, 96.2)	334	0.0 to 282.1	63.5	70.0	85.2 (78.4, 92.1)
	≥70	193	0.0 to 243.9	69.1	78.0	92.4 (82.6, 102.2)	308	0.0 to 293.0	70.2	91.6	98.9 (91.1, 106.8)
	All	315	0.0 to 287.4	68.1	74.4	89.3 (81.7, 96.8)	642	0.0 to 293.0	67.1	80.0	91.8 (86.6, 97.0)
30-90	60 to 69	122	0.0 to 416.1	72.8	0.0	31.8 (18.8, 44.9)	334	0.0 to 535.9	80.6	1.3	33.4 (24.7, 42.1)
	≥70	193	0.0 to 524.5	96.6	2.1	47.5 (33.8, 61.3)	308	0.0 to 600.0	133	4.1	75.3 (60.4, 90.2)
	All	315	0.0 to 524.5	88.3	1.0	41.5 (31.7, 51.2)	642	0.0 to 600.0	111	2.6	53.5 (44.9, 62.1)
90-182	60 to 69	122	0.0 to 534.6	60.8	0.0	10.9 (-0.0, 21.8)	334	0.0 to 914.0	80.6	0.0	15.8 (7.1, 24.4)
	≥70	193	0.0 to 617.7	78.1	0.0	19.9 (8.8, 31.0)	308	0.0 to 920.0	141	0.0	50.4 (34.5, 66.2)
	All	315	0.0 to 617.7	71.9	0.0	16.4 (8.4, 24.4)	642	0.0 to 920.0	115	0.0	32.4 (23.5, 41.3)
0-182	60 to 69	122	0.0 to 1238.0	163	73.5	127.1 (97.9, 156.2)	334	0.0 to 1712.5	186	75.8	134.4 (114.3, 154.4)
	≥70	193	0.0 to 1330.2	206	85.5	159.8 (130.6, 189.0)	308	0.0 to 1813.0	306	110.5	224.6 (190.3, 258.9)
	All	315	0.0 to 1330.2	190	82.5	147.1 (126.0, 168.2)	642	0.0 to 1813.0	255	87.8	177.7 (157.9, 197.4)

MITT: All randomized subjects who were followed ≥30 days postvaccination and did not develop evaluable cases of HZ (per the hierarchical algorithm specified in Protocol Amendment 6) within the first 30 days postvaccination.
Severity-by-duration score was defined as the area under the worst pain response (rated on a 0 to 10 scale) versus time curve during the 6-month period following HZ rash onset.
N = Number of subjects randomized. n = Number of evaluable HZ cases in the MITT population. HZ = Herpes zoster.
MITT = Modified intention-to-treat. CI = Confidence interval. SD = Standard deviation.

(Source: STN 125123, Protocol 004 Tables 7-22 and 11-58)

Additional Safety Data

Table 11-5 Clinical AEs Days 0-42 Postvaccination by Gender in AE Monitoring Substudy

	Zoster Vaccine (N – 3345)				Placebo (N = 3271)			
	Female		Male		Female		Male	
	n	(%)	N	(%)	n	(%)	n	(%)
Number of subjects Subjects with safety follow-up Subjects without safety follow-up	1515 1508 7		1830 1818 12		1424 1415 9		1847 1834 13	
No adverse experience (AE)	441	29.24	956	52.59	905	63.96	1227	66.90
One or more AE	1067	70.76	862	47.41	510	36.04	607	33.10
Injection-site AE	950	63.00	654	35.97	280	19.79	259	14.12
Systemic AE (SAEs)	425	28.18	395	21.73	335	23.67	433	23.61
Vaccine-related AE†	975	64.66	691	38.01	331	23.39	309	16.85
Injection-site AE‡	949	62.93	653	35.92	279	19.72	257	14.01
Systemic AE	130	8.62	79	4.35	82	5.80	78	4.25
Serious AE (SAEs)	16	1.06	48	2.64	8	0.57	33	1.80
Serious vaccine-related AE†	0	0.00	0	0.00	0	0.00	1	0.05
Died	0	0.00	3	0.17	0	0.00	2	0.11
Discontinuations:								
Due to an AE	0	0.00	0	0.00	0	0.00	0	0.00
Due to a vaccine-related AE†	0	0.00	0	0.00	0	0.00	0	0.00
Due to a SAE	0	0.00	0	0.00	0	0.00	0	0.00
Due to a vaccine-related SAE†	0	0.00	0	0.00	0	0.00	0	0.00

†Determined possibly, probably, or definitely vaccine-related by investigator.
‡All injection-site adverse experiences reported regardless of investigator assessment.
N = Number of subjects vaccinated in the Adverse Event Monitoring Substudy.
n = Number of subjects in the respective category.

(Source: STN 125123, Protocol 004 Table 11-124)

Table 11-6 Systemic Events in AE Monitoring Substudy Days 0-42

	Zoster Vaccine (N = 3345)		Placebo (N = 3271)		Estimated Risk Difference‡ in Percentage Points (95% CI)‡
	n	Estimated Risk† (%)	n	Estimated Risk† (%)	
Number of subjects	3345		3271		
Subjects with safety follow-up	3326		3249		
Subjects w/out safety follow-up	19		22		
Number (%) of subjects w/ ≥1 systemic adverse experiences	820	(24.7)	768	(23.6)	
Cardiovascular	40	(1.2)	38	(1.2)	0.0 (-0.5, 0.6)
Digestive	124	(3.7)	122	(3.8)	-0.0 (-1.0, 0.9)
Diarrhea	51	(1.5)	41	(1.3)	0.3 (-0.3, 0.9)
General body	350	(10.5)	319	(9.8)	0.7 (-0.7, 2.2)
Fever	59	(1.8)	53	(1.6)	0.1 (-0.5, 0.8)
Flu syndrome	57	(1.7)	52	(1.6)	0.1 (-0.5, 0.7)
Headache	89	(2.7)	85	(2.6)	0.1 (-0.7, 0.9)
Pain	53	(1.6)	60	(1.8)	-0.2 (-0.9, 0.4)
Musculoskeletal	48	(1.4)	39	(1.2)	0.2 (-0.3, 0.8)
Nervous system	57	(1.7)	58	(1.8)	-0.1 (-0.7, 0.6)
Respiratory	238	(7.2)	203	(6.2)	0.9 (-0.3, 2.1)
Infection	65	(2.0)	55	(1.7)	0.3 (-0.4, 0.9)
Pharyngitis	59	(1.8)	57	(1.8)	0.0 (-0.6, 0.7)
Respiratory disorder	35	(1.1)	27	(0.8)	0.2 (-0.3, 0.7)
Rhinitis	46	(1.4)	36	(1.1)	0.3 (-0.3, 0.8)
Skin	252	(7.6)	237	(7.3)	0.3 (-1.0, 1.6)
Pruritus	42	(1.3)	40	(1.2)	0.0 (-0.5, 0.6)
Rash	63	(1.9)	65	(2.0)	-0.1 (-0.8, 0.6)
Rash, macular, papular	36	(1.1)	35	(1.1)	0.0 (-0.5, 0.5)
Skin disorder	35	(1.1)	31	(1.0)	0.1 (-0.4, 0.6)

†Estimated risk: calculated as a weighted average of the observed risks stratified by age group w/ weights proportional to total numbers of subjects w/AE follow-up in each age group.
‡Risk difference: calculated by subtracting estimated risk for placebo group from estimated risk for zoster vaccine group. CI of risk difference is computed based on an asymptotic method for difference of two binomial proportions.
Adverse Event Monitoring Substudy:
1. Vaccination Report Cards (VRCs) recorded daily adverse experiences occurring Days 0-42
2. Contact around Day 43 to capture any additional AEs or cases of HZ not already reported to the study site.
3. Monthly follow-up using ATRS to capture signs/symptoms of HZ & occurrence of hospitalization.

Subjects w/ ≥1 safety follow-up contact Days 0-42 considered to have safety follow-up for period.
Subject may have had ≥2 AEs in an AE category, but is counted only once w/in that AE category. The same subject may appear in different adverse experience categories.
All body systems are listed in which at least 1 subject had an adverse experience.
N = Number of subjects vaccinated in the Adverse Event Monitoring Substudy.
n = Number of subjects in the respective category.
CI = Confidence interval. ATRS = Automated telephone response system.
AE terms are from COSTART Version 2; conditions not captured by COSTART assigned corresponding term from Case Report Form.

(Source: STN 125123, Protocol 004 Table 11-133)

Additional Immunogenicity Data

Table 11-7 Analysis of IFN-γ ELISPOT Counts at 6 Weeks Postvaccination in CMI Substudy

	Zoster Vaccine (N=691)		Placebo (N=704)		Fold Difference† [Zoster/Placebo]
Endpoint	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)

†Based on analysis of covariance (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.
N = Number of subjects vaccinated in the CMI Substudy.
n = Number of subjects contributing to immunogenicity analysis (valid results at baseline and 6 week postvaccination).
VZV = Varicella-zoster virus
ELISPOT = Enzyme-linked immunospot. The ELISPOT count is the number of spot-forming cells per 106PBMC.
CMI = Cell mediated immunity GMC = Geometric mean count CI = Confidence interval.
PBMC = Peripheral blood mononuclear cells IFN = Interferon.

Source: STN 125123, Protocol 004, Table 7-59

Table 11-8 Effect of Age, Gender, Study Site, Prevaccination Immune Status, Timing of Postvaccination Blood Sample & Vaccine Potency on IFN- γ ELISPOT Response - 6 Weeks Postvaccination, CMI Substudy

	Treatment	Age	Gender	Study Site	Log- Transformed Prevaccination VZV IFN-γELISPOT Counts	Timing of the Postvaccination Blood Sample	Potency Subjects Received (PFU/Dose)
Regression Coefficient Estimate†	0.894	-0.024	0.097	-0.454	0.492	-0.023	-0.000
Coefficient Standard Error†	0.423	0.006	0.077	0.078	0.024	0.008	0.000
p-value†	0.035	<0.001	0.206	<0.001	<0.001	0.006	0.808

†Computed using an ANCOVA model in which natural-log-transformed VZV IFN-γELISPOT count at 6 weeks postvaccination was the response variable, and vaccination group, age, gender, study site, potency subjects received, natural-log-transformed prevaccination VZV IFN-γELISPOT count and timing of postvaccination blood sampling were the covariates. VZV = Varicella-zoster virus. ELISPOT = Enzyme-linked immunospot. The ELISPOT count is the number of spot-forming cells per 106PBMC. CMI = Cell mediated immunity. PBMC = Peripheral blood mononuclear cells. IFN = Interferon.

(Source: STN 125123, Protocol 004, Table 7-60)

Table 11-9 Analysis of RCF Responses at 6 Weeks Postvaccination in CMI Substudy

Endpoint	Zoster Vaccine (N=691)		Placebo (N=704)		Fold Difference† [Zoster/Placebo]
	n	Estimated Response†	n	Estimated Response†	(95% CI)
GMV	642	9.9	662	5.2	1.9 (1.7,2.1)
Geometric Mean Fold Rises from Day 0	642	1.7	662	0.9	1.9 (1.7,2.1)

†Calculated based on an analysis of covariance (ANCOVA) model, which included the natural-log-transformed RCF Value 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 RCF value at Day 0 as independent variables. The fold differences for both GMV 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 0.8075.
N = Number of subjects vaccinated in the CMI Substudy.
n = Number of subjects contributing to this analysis (valid results at baseline & 6 week postvaccination).
RCF = Responder cell frequency. RCF value is the number of responder cells per 105PBMC.
VZV = Varicella-zoster virus.
CMI = Cell mediated immunity.
GMV = Geometric mean value.
CI = Confidence interval.

Source: STN 125123, Protocol 004, Table 7-63

Table 11-10 Persistence of Immune Responses Among CMI Substudy Participants

Endpoint	Time Point	Zoster Vaccine (N=691)			Placebo (N=704)		
		N	Observed Response	95% CI	n	Observed Response	95% CI
VZV IFN-γ ELISPOT Counts							
GMC	Day 0	607	34.5	(30.3, 39.1)	629	34.2	(30.2, 38.7)
	6 Weeks	606	72.0	(63.5, 81.6)	642	31.6	(28.0, 35.6)
	12 Months	635	92.7	(84.0, 102.3)	655	59.2	(53.5, 65.3)
	24 Months	647	87.2	(79.5, 95.6)	644	58.6	(52.9, 64.9)
	36 Months	614	76.4	(68.6, 85.0)	603	47.0	(41.7, 53.0)
Geometric Mean Fold Rises From Day 0	6 Weeks	582	2.0	(1.8, 2.3)	611	0.9	(0.8, 1.1)
	12 Months	560	2.6	(2.3, 2.9)	585	1.7	(1.5, 1.9)
	24 Months	570	2.4	(2.2, 2.7)	580	1.7	(1.5, 1.9)
	36 Months	543	2.2	(1.9, 2.5)	541	1.3	(1.1, 1.5)
VZV RCF Values							
GMV	Day 0	664	5.7	(5.3, 6.2)	678	5.8	(5.4, 6.3)
	6 Weeks	668	9.7	(9.0, 10.4)	687	5.3	(4.9, 5.8)
	12 Months	592	6.1	(5.7, 6.6)	597	4.3	(3.9, 4.7)
	24 Months	451	6.2	(5.6, 6.8)	444	4.4	(3.9, 4.9)
	36 Months	627	4.4	(4.0, 4.8)	623	3.3	(3.0, 3.7)
Geometric Mean Fold Rises From Day 0	6 Weeks	642	1.7	(1.6, 1.8)	662	0.9	(0.8, 1.0)
	12 Months	576	1.0	(0.9, 1.1)	580	0.7	(0.6, 0.8)
	24 Months	435	1.2	(1.1, 1.4)	428	0.9	(0.8, 0.9)
	36 Months	604	0.7	(0.7, 0.8)	600	0.6	(0.5, 0.6)
gpELISA Titers							
GMT	Day 0	678	278.8	(258.0, 301.4)	691	291.0	(269.7, 314.0)
	6 Weeks	667	474.7	(441.5, 510.5)	684	291.4	(269.3, 315.3)
	12 Months	649	353.7	(328.1, 381.2)	661	306.6	(283.3, 331.9)
	24 Months	636	329.5	(304.5, 356.5)	644	300.6	(277.8, 325.3)
	36 Months	625	331.6	(305.1, 360.4)	612	305.7	(280.6, 333.2)
Geometric Mean Fold Rises From Day 0	6 Weeks	655	1.7	(1.6, 1.8)	673	1.0	(1.0, 1.0)
	12 Months	636	1.3	(1.2, 1.3)	650	1.1	(1.0, 1.1)
	24 Months	624	1.2	(1.1, 1.2)	633	1.1	(1.0, 1.1)
	36 Months	612	1.2	(1.1, 1.3)	601	1.0	(1.0, 1.1)

N = # subjects vaccinated in CMI Substudy. n = # subjects contributing to immunogenicity analysis.
VZV = Varicella-zoster virus.
ELISPOT = Enzyme-linked immunospot. ELISPOT count = number of spot-forming cells per 10^6PBMC.
RCF = Responder cell frequency. RCF value is the number of responder cells per 105 PBMC.
GMV = Geometric mean value.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
GMT = Geometric mean titer. CMI = Cell mediated immunity.
GMC = Geometric mean count. PBMC = Peripheral blood mononuclear cells.
CI = Confidence interval. IFN = Interferon.

(Source: STN `125123, Protocol 004, Table 7-69-71

Vaccine effect explained by ELISPOT count was lower (15.7%) than the proportions explained by RCF value (24.4%) or gpELISA titer (45.9%). This may in part be the result of relatively large ELISPOT assay variability.

Table 11-11 Effect of Age, Gender, Study Site, Prevaccination Immune Status, Postvaccination Timing, Blood Sample, and Vaccine Potency on gpELISA Titers at 6 Weeks Postvaccination

	Treatment	Age	Gender	Study Site	Log-Transformed Prevaccination gpELISA Titers	Timing of the Postvaccination Blood Sample	Potency Subjects Received (PFU/Dose)
Regression Coefficient Estimate†	0.306	-0.006	0.014	-0.048	0.788	-0.009	0.000
Coefficient Standard Error†	0.178	0.003	0.033	0.033	0.016	0.003	0.000
p-value†	0.085	0.021	0.681	0.148	<0.001	0.012	0.243

†Computed using an ANCOVA model in which natural-log-transformed gpELISA titers at 6 weeks postvaccination were the response variable, and vaccination group, age, gender, study site, potency subjects received, natural-log-transformed prevaccination gpELISA titers and timing of the postvaccination blood sample were the covariates. gpELISA = Glycoprotein enzyme-linked immunosorbent assay. CMI = Cell mediated immunity.

(Source: STN 125123, Protocol 004 Table 7-66)

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