UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE MEETING

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THURSDAY, DECEMBER 15, 2005

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The meeting came to order at 9:00 a.m. in the Versailles Ballroom of the Holiday Inn Select, 8120 Wisconsin Avenue, Bethesda, MD, Gary D. Overturf, Chairman, presiding.

PRESENT:

GARY D. OVERTURF, M.D.	Chairman
CHRISTINE WALSH, R.N.	Ex. Secretary
MONICA M. FARLEY, M.D.	Member
RUTH A. KARRON	Member
DAVID MARKOVITZ, M.D.	Member
WALTER ROYAL, III, M.D.	Member
BONNIE M. WORD, M.D.	Member
THOMAS FLEMING, Ph.D.	Temp. Voting Member
BRUCE GELLIN, M.D., M.P.H.	Temp. Voting Member
MICHAEL ROWBOTHAM, M.D.	Temp. Voting Member
DANIEL SCHARFSTEIN, SC.D.	Temp. Voting Member
MELINDA WHARTON, M.D., M.P.H.	Temp. Voting Member
SETH HETHERINGTON, M.D.	Acting Industry Rep.

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P-R-O-C-E-E-D-I-N-G-S

9:03 a.m.

CHAIRMAN OVERTURF: Good morning, I would like to call the meeting to order and first of all, I'll turn it over to Christine Walsh, the Executive Secretary, for some administrative issues.

MS. WALSH: Good morning. I'm Christine Walsh, the Executive Secretary for today's meeting of the Vaccines and Related Biological Products Advisory Committee. I would like to welcome all of you to this meeting of the Advisory Committee.

Today's session will consist of presentations that are open to the public. I would like to request that everyone, please, check your cell phones and pagers to make sure they are off or in the silent mode. Due to a family emergency, Dr. Pamela McInnes will be unable to attend the meeting with us today.

I would now like to read into the public record the Conflict of Interest statement for today's meeting. "This brief announcement is in addition to the Conflict of Interest statement read at the

beginning of the meeting on December 14th and will be part of the public record for the Vaccines and Related Biological Products Advisory Committee meeting on December 15, 2005.

This announcement addresses Conflicts of Interest for the discussions of Topic 2 on the Safety and Efficacy of ZOSTAVAX manufactured by Merck and Company. Dr. Steven Self has recused himself from the discussion of Topic 2, Safety and Efficacy of ZOSTAVAX. In accordance with 18 USC Section 208(b)(3), waivers have been granted to Drs. Ruth Karron, Thomas Fleming and Daniel Scharfstein.

Dr. Ruth Karron for unrelated consulting with the competitor for which she receives less than $10,000 per year. Dr. Thomas Fleming for unrelated consulting with a competitor for which he receives less than $10,001 per year. Dr. Daniel Scharfstein for unrelated consulting with a competitor for which he receives less than $10,001 per year and ownership of stock in the sponsor currently valued at less than $10,001.

A copy of the written waiver statement may

be obtained by submitting a written request to the Agency's Freedom of Information office, Room 12A-30 of the Parklawn Building. Dr. Seth Hetherington is serving as the industry representative acting on behalf of all related industry and is employed by Inhibitex Incorporated. Industry representatives are not special Government employees and do not vote.

In addition, there are regulated industry speakers making presentations. These speakers may have financial interest associated with their employer and with other regulated firms. The FDA asks in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

These individuals were not screened by the FDA for conflicts of interest. This Conflict of Interest statement will be available for review at the registration table. We would like to remind Members and consultants that if the discussions involved any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude

themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships that you may have with the sponsor, its product and, if known, its direct competitors." That ends the reading of the Conflict of Interest statement. Dr. Overturf, I turn the meeting back over to you.

CHAIRMAN OVERTURF: Again, I would like to welcome you to this meeting of VRBPAC for December 15th and I would like to go around the Committee Members and ask them to introduce themselves again and, please, tell us where you are from. Dr. Karron, we'll start with you.

MEMBER KARRON: Ruth Karron, Johns Hopkins University.

DR. FLEMING: Thomas Fleming, University of Washington.

MEMBER WORD: Bonnie Word, Baylor College of Medicine.

DR. SCHARFSTEIN: Daniel Scharfstein, Johns Hopkins University.

DR. ROWBOTHAM: Mike Rowbotham, University of California San Francisco.

DR. GELLIN: Bruce Gellin, National Vaccine Program Office, HHS.

DR. WHARTON: Melinda Wharton, National Immunization Program, Centers for Disease Control and Prevention.

MEMBER ROYAL: Walter Royal, University of Maryland School of Medicine.

DR. HETHERINGTON: Seth Hetherington, Inhibitex in Alpharetta, Georgia.

MEMBER FARLEY: Monica Farley, Emory University School of Medicine.

MEMBER MARKOVITZ: David Markovitz at University of Michigan.

CHAIRMAN OVERTURF: And I'm Dr. Gary Overturf from the University of New Mexico. So we will begin the meeting today which is to evaluate the safety and efficacy of ZOSTAVAX and I'll ask Patricia Rohan to come forward and provide the introduction from the FDA.

DR. ROHAN: Dr. Overturf, good morning,

personnel from Merck, invitees, Committee, I would like to welcome you all. I'm the medical officer and I'll be speaking later for this presentation, but first we would like to as usual go over the Committee's questions that will be considered later this afternoon.

Question No. 1: "Are the available data adequate to support the efficacy of ZOSTAVAX when administered to individuals 50 years of age and older in preventing herpes zoster, in preventing postherpetic neuralgia, preventing postherpetic neuralgia beyond the effect on the prevention of herpes zoster and decreasing the burden of illness and decreasing the burden of illness beyond the effect on the prevention of herpes zoster and, if not, what additional information should be provided?"

Question No. 2: "Are the available data adequate to support the safety of ZOSTAVAX when administered to persons 50 years of age and older, if not, what additional information should be provided?"

Question No. 3: "Please, identify other issues that should be addressed, including post-

licensure studies. In particular, please, address the use of the vaccine in persons with co-morbid conditions. For example, those who might typically reside in assisted living residences and nursing homes. The use of the vaccine among persons taking chronic immunosuppressive agents, such as corticosteroids, the use of the vaccine in certain subjects of the sponsor's proposed age indication. For example, those 70 years of age and older, those 80 years of age and older. The duration of immunity and a sponsor's proposed pharmacovigilance plan." Thank you.

CHAIRMAN OVERTURF: Thank you, Dr. Rohan. We will begin now with the sponsor's presentation.

DR. GUTSCH: Good morning, Mr. Chairman, Members of the Advisory Committee, the FDA, ladies and gentlemen. My name is David Gutsch and I'm a Director in the Department of Regulatory Affairs at Merck Research Laboratories. Today I'm going to start by introducing you to ZOSTAVAX, the Merck vaccine, for the prevention of herpes zoster and its complications including postherpetic neuralgia or PHN.

As you will hear today, there is a medical need for a vaccine to prevent herpes zoster and its complications. Herpes zoster is common in those 50 years of age and older. There is no medical intervention to prevent herpes zoster. The acute and chronic pain associated with herpes zoster is often severe and debilitating. And with available therapies, management of the acute and long-lasting pain complicating herpes zoster can be frustrating.

The hypothesis for the ZOSTAVAX Program is that vaccination with the live attenuated Oka/Merck VZV vaccine will meet an important unmet medical need by reducing the incidence of herpes zoster, otherwise known as shingles, and by reducing the frequency and/or severity of herpes zoster of the complications of herpes zoster, including postherpetic neuralgia, the pain that can last for months to years after a rash heals.

As you will see in the following presentation, there are many definitions of postherpetic neuralgia in the literature, including pain persisting beyond rash healing through pain

persisting beyond six months. Based on the literature and consultation with experts for the purposes of the ZOSTAVAX clinical studies, PHN was defined as the presence of clinically significant pain present 90 days or more after herpes zoster rash onset.

ZOSTAVAX is a live attenuated varicella-zoster vaccine, varicella-zoster virus vaccine, that uses the same Oka/Merck strain that is present in VARIVAX, the licensed vaccine for chicken pox, and the recently licensed ProQuad for measles, mumps, rubella and varicella. And while VARIVAX and ProQuad contain the same active ingredient, there are notable differences in these products.

VARIVAX is used for the primary prevention of VZV and, therefore, is administered to younger VZV naive population. The proposed use of ZOSTAVAX is for prevention of reactivation of VZV and the subsequent complications of that reactivation. So ZOSTAVAX would be targeted to an older population. ZOSTAVAX is a preservative-free lyophilized product that is administered as a single subcutaneous dose.

ZOSTAVAX is manufactured using the same

process as VARIVAX and both vaccines contain the same excipients. When reconstituted and administered as instructed, ZOSTAVAX contains 19,400 plaque-forming units per dose, which is about 14 times the dose present in VARIVAX in order to list at the desired immune response.

The proposed indications for ZOSTAVAX are as follows: ZOSTAVAX is indicated for the prevention of herpes zoster or shingles, prevention of postherpetic neuralgia, reduction of acute and chronic zoster-associated pain. ZOSTAVAX is indicated for immunization of individuals 50 years of age and older. As you will hear in more detail, these three clinically meaningful indications are directly supported by having met the success criteria for key Shingles Prevention Study efficacy endpoints that were pre-specified and mutually agreed upon by the sponsor and the FDA.

The three endpoints that support the indications regarded the decrease incidence of herpes zoster, decreased incidence of postherpetic neuralgia and reduction of the pain burden of illness over a six

month follow-up period after herpes zoster rash onset. Although the Shingles Prevention Study enrolled subjects 60 years of age and older, there is a strong case for vaccination with ZOSTAVAX starting at age 50. The next speaker will take you through the epidemiologic and clinical evidence supporting the proposed target age range.

In the ZOSTAVAX vaccine license application there are eight clinical trials in which ZOSTAVAX has been administered, including the Shingles Prevention Study of Veterans Affairs, Cooperative Studies Program, Multicenter Placebo-Controlled Study in which nearly 40,000 subjects were enrolled. And as you will see, these studies demonstrated that ZOSTAVAX is efficacious in preventing herpes zoster and PHN in reducing the overall burden of zoster-associated pain, including severe pain, and in reducing the interference with activities of daily living due to herpes zoster.

Furthermore, you will see that ZOSTAVAX is immunogenic in the VZV experience vaccinees and that ZOSTAVAX has an excellent safety profile.

Collectively, the efficacy, immunogenicity and safety that results support a favorable risk/benefit assessment as an intervention to prevent herpes zoster and its complications, including PHN, ZOSTAVAX represents a major medical advance.

There are several collaborators present who are associated with the Shingles Prevention Study, the large pivotal study in support of ZOSTAVAX. Here today are Dr. Michael Oxman, Study Chairman for the Shingles Prevention Study; Gary Johnson, a Shingles Prevention Study Biostatistician; and Dr. Myron Levin, a key principle investigator. Also present as clinical consultants are Dr. Ann Arvin, Dr. David Cornblath, Dr. Robert Johnson and Dr. David Weber. And our statistical consultants are Dr. James Neaton and Dr. Janet Wittes.

A detailed briefing document was previously provided to the Advisory Committee Members. Dr. Jeffrey Silber from the Department of Clinical Research at Merck Research Laboratories will now present the highlights of the information provided in the briefing document. Following this, I will provide

some concluding remarks.

DR. SILBER: Thank you, David, and good morning. This morning I have the privilege of sharing with you information on a number of topics. The epidemiology of herpes zoster and postherpetic neuralgia, an overview of the Clinical Development Program for ZOSTAVAX followed by a more detailed description of the study design and key results from the Shingles Prevention Study. I will also review available immunogenicity and safety data for the product before providing an overall summary of the clinical trial results.

As background, it is important to note that herpes zoster, commonly known as shingles, is a clinical manifestation of the reactivation of latent infection with varicella-zoster virus or VZV. Primary infection with VZV typically in childhood causes chicken pox. Thereafter, the virus establishes a latent infection in the dorsal root ganglion of the spinal cord where it remains quiescent for many years.

In the United States nearly all adults have evidence of prior VZV infection and therefore are

at risk for shingles. During prolonged latency, VZV-specific cellular immunity keeps the virus in check. And for reasons that are not entirely understood, but are clinically associated with advancing age or immunosuppression, the virus reactivates.

The virus travels down the nerve root, reaches the skin and develops into the characteristic eruption of painful, erythematous, maculopapular lesions that evolve into clustered fluid-filled vesicles that are shown on the right hand side in a pathognomonic dermatomal distribution.

Herpes zoster is a relatively common disease. It is estimated that, approximately, 1 million cases of herpes zoster occur each year in the United States, of which nearly two-thirds occur in persons over the age of 50. And this number is expected to rise due to the aging of the population. An estimated 50,000 to 60,000 hospitalizations each year in the United States include a diagnosis of herpes zoster. And among these are an estimated 12,000 to 19,000 for which herpes zoster is the primary diagnosis.

Of note, 85 to 90 percent of all herpes zoster cases and 70 to 80 percent of hospitalizations occur in immunocompetent individuals. And it has been noted in recent studies that the lifetime risk of developing herpes zoster may be as high as about 30 percent and for those who attain the age of 85, up to 50 percent will have suffered one or more episodes of zoster in their lifetime.

Although herpes zoster has been noted to occur after stressful life events or the site of prior physical trauma, the only clearly established risk factors for herpes zoster are increasing age and immunosuppression. This figure is from a classic paper by Hope-Simpson showing the age-related contributions in herpes zoster and postherpetic neuralgia or PHN. I'll be speaking much more about PHN in subsequent slides.

In this figure, the X axis shows age in years and on the Y axis is the rate of disease. And you will note that there is a substantial increase in the incidence of postherpetic neuralgia beginning at age 60, whereas the incidence of herpes zoster begins

to rise fairly dramatically at age 50. Similar findings have been borne out from more recently conducted population-based studies.

This slide shows the number and the proportion of all herpes zoster cases in the United States across the different decades of life, based on the most recent census data and the age-specific rates from the Hope-Simpson Study. And the results are generally similar when results of other population-based studies are applied. Note the preponderance of herpes zoster cases among the older adults with the number of cases among people in their 50s at least as high as among people in their 60s, a phenomena that is expected to continue.

The next two slides show typical herpes zoster eruptions. The first shows a herpes zoster case in a mid-thoracic dermatome. The lesions of herpes zoster are typically unilateral, but can cross the midline slightly and can also cross into adjoining dermatomes. The skin lesions usually evolve over about 7 to 10 days and then heal over the subsequent two to three weeks.

The following slide shows an episode later in its course, an ophthalmic zoster in the ophthalmic distribution of the fifth cranial nerve. After the thorax, the fifth cranial nerve is the most common location for herpes zoster to occur. Herpes zoster ophthalmic represents 10 to 15 percent of all herpes zoster cases and about 50 percent of those have ocular involvement. Sight threatening complications can ensue and so prompt attention to these cases is essential.

Numerous complications can result from an episode of herpes zoster. The most common neurologic manifestation is acute neuritic pain, which affects over 90 percent of all episodes of herpes zoster, and can be quite severe even in younger individuals. Postherpetic neuralgia, which is generally defined as pain present following resolution of the rash, is a relatively frequent complication that increases with age, and more on this later.

Other neurologic complications include loader motor neuron palsies, which can affect up to 5 percent of episodes, sensory deficits, autonomic

dysfunction and more rarely meningitis, myelitis or encephalitis. A number of ocular complications can occur as a result of ophthalmic zoster as shown on the previous slide. Among the cutaneous complications of zoster are scarring and bacterial superinfection most commonly with staph and strep.

In immunocompromised individuals, visceral complications can occur, including disseminated disease, which carries a mortality rate of up to 40 percent. Although the rash is the most characteristic feature of acute herpes zoster, the most troubling symptom is pain. A majority of patients with herpes zoster first experience prodromal pain of varying duration and the symptoms can also include tingling, itching or burning.

As shown here, the pain during both the acute herpes zoster episode and the postherpetic phase can be quite severe. Patients frequently compare it to the pain associated with child-birth or passing a kidney stone. Early in its course, herpes zoster can be mistaken for a number of other clinical diseases that are common in older adults, including myocardial

infarction, cholecystitis, kidney stone, migraine or other CNS condition or severe musculoskeletal pain.

Almost half of all patients with herpes zoster experience pain on a daily basis during the episode and a similar percentage described that pain as horrible or excruciating.

Postherpetic neuralgia is residual pain that is present after resolution of the acute cutaneous eruption of herpes zoster. The pain of PHN can be constant or intermittent, dull and achy, burning, sharp and stabbing or shock-like. And most patients with PHN describe more than one pattern of pain. A particularly common and distressing symptom, which affects a majority of PHN patients, is allodynia.

The exaggerated pain experienced in response to otherwise benign stimulus like the breeze, a bedsheet or just the touch of clothing, often leads to sleep disturbance, social isolation and depression. Overall 10 to 20 percent of herpes zoster patients develop PHN, but the incidence increases dramatically with age. The impact of PHN can be profound leading

to physical, psychological, social and functional deficits as well as increased use of health care resources.

Particularly in older adults, PHN can last for months or even years. It is estimated that the prevalence of PHN in the United States is as high as 500,000 or more, which is nearly as high as the prevalence of diabetic neuropathy as a cause of neuropathic pain. As mentioned by Dr. Gutsch, the Pivotal Efficacy Study for ZOSTAVAX implied a specific and rigorous definition of PHN.

This slide from the era before the availability of antivirals looks at postherpetic pain by age and makes several interesting points. The findings are not terribly different today for older adults with herpes zoster. First, note that postherpetic pain of at least a month's duration is rather common, even in middle-aged adults, but that it is very common in the oldest patients. Second, prolonged pain of a year or more becomes more common among the oldest individuals.

Antiviral medications have been shown to

reduce the severity of acute herpes zoster and in some patients the medications can shorten the duration of the acute episode by a few days. However, the drugs need to be started within the first 72 hours of onset to have maximum effect. Also, antivirals have only a limited effect on the incidence or the severity of PHN once an episode of herpes zoster has begun.

Corticosteroids have often been used in acute herpes zoster, either alone or in conjunction with antivirals, and the corticosteroids may ameliorate the acute episode, but they have not been shown to affect either the incidence or the severity of PHN. Once PHN develops, finding effective treatment can be challenging, in part because of the wide variation in the type and intensity of the individual's symptoms.

Among the available therapies for PHN are a variety of topical and systemic analgesics, including opiates, tricyclic antidepressants, drugs with anticonvulsant properties and a number of invasive procedures. In general, these interventions have been shown to have limited benefit for patients

with PHN and some patients are completely refractory to multiple interventions.

In addition, these agents often have narrow therapeutic indices. They are often associated with limiting side effects, particularly in elderly patients, that make their continued use problematic. The published literature shows that the risk of herpes zoster and PHN goes up substantially after age 50 and there are, approximately, 87 million people in the United States in this age group, and this is a number that will only rise with time.

As just pointed out, the handful of currently available therapies have only moderate benefits and sometimes significant limitations. No intervention can reliably prevent shingles or PHN. Because herpes zoster is more frequent and more severe as age increases and because VZV-specific immunity is known to decline with age, then if VZV-specific immunity could be boosted with vaccination, herpes zoster could be prevented or ameliorated.

For these reasons, ZOSTAVAX has been developed and is expected to have a dramatic public

health impact in the United States. I would like to turn now to the ZOSTAVAX Clinical Development Program. The hypothesis that vaccination could prevent herpes zoster, ameliorate its severity and potentially prevent PHN comes from two proof of concept studies that were conducted by Ann Arvin and her colleagues at Stanford University using a heat inactivated formulation of the Oka/Merck VZV vaccine to vaccinate immunocompromised patients in a multi-dose regimen.

The first study published in 1997 show that the vaccine had good biological activity. Although the incidents of herpes zoster was not reduced among those who were vaccinated, the vaccine did reduce the incidence of PHN and significantly ameliorated the severity of herpes zoster. Based on the results of this study and other pilot studies, the efficacy trial was designed originally with pain-related primary endpoints and so-focused on the age group 60 and above in whom zoster-associated pain and PHN are most severe.

In a follow-up study, the results of which became available when enrollment in the pivotal study

was complete and follow-up was continuing, Arvin's group found for the first time that vaccination could significantly reduce the incidence of herpes zoster outright.

The licensed application for ZOSTAVAX includes a number of studies that are outlined on this slide. The first two were dose selection studies that established the safety of the vaccine over a 35-fold range of potencies and also explored immune responses using a number of potential markers. Efficacy was evaluated in the pivotal Shingles Prevention Study, which will form the bulk of the remainder of my talk.

Other studies in the program included evaluation of a two-dose regimen and a booster study in individuals who received vaccine years earlier. Additional safety evaluations included vaccination of a small number of VZV-seronegative adults and a study that compared the vaccine at maximum potency with a potency similar to that studied in other clinical trials. In all, about 21,000 subjects received one or more doses of ZOSTAVAX and nearly as many placebo recipients were enrolled in well-controlled clinical

trials.

I would like to spend a moment discussing the potency range that was studied in the program, and in particular, the prospect of assessment that led to the potencies that were evaluated in the Shingles Prevention Study.

Across the program, vaccine was administered across, approximately, a 100-fold range of potencies. In addition to demonstrating an adequate safety profile, the early studies suggested that potencies of, approximately, 17,000 plaque-forming units or higher resulted in a boost in VZV-specific immunity and thus formed the basis for selecting a target minimum potency of 19,000 plaque-forming units for the efficacy trial.

ZOSTAVAX has been studied in a large number of older adults reflecting the target population for the vaccine. The vaccine has been administered to individuals as young as 30 and as old as 99 with a wide array of underlying medical conditions. About 58 percent of the subjects enrolled were male. Over 95 percent of the study population

was caucasian, but the database also includes over 400 African Americans, about 300 Hispanic subjects and a number of subjects from other racial and ethnic minorities. Except for some age related findings that we presented in subsequent slides, no differences in the efficacy, immunogenicity or safety of the vaccine were seen across demographic groups.

I would now like to turn to an in-depth description of the Shingles Prevention Study. The Shingles Prevention Study, the results of which were published in the New England Journal of Medicine earlier this year was a double-blind placebo-controlled multicenter trial conducted by the Department of Veteran Affairs Cooperative Studies Program in collaboration with the National Institute of Allergy infectious diseases of NIH and Merck.

The study enrolled 38,546 individuals 60 years of age and older. Enrollment was stratified by age to ensure that at least one-third of the subjects enrolled would fall in the 70 plus age group. Nearly 90 percent of the enrolled subjects had one or more underlying medical conditions, but those with known

immunocompromised were excluded. Nearly half of the patients or subjects noted some limitations in their daily function from their medical illnesses with about 10 percent moderately or severely limited.

Enrolled subjects were randomized 1:1 to receive ZOSTAVAX or a placebo injection that was made up of the vaccine's stabilizer and uninfected cells. Most of the doses in the study were administered near the proposed expiry potency and after enrollment, follow-up to identify suspected cases of herpes zoster, monitor safety and ensure subject retention was undertaken through use of monthly telephone contacts and a final closeout interview.

As shown on the slide, although a majority of the subjects enrolled in the study were at VA medical centers, the overall enrollment was reasonably well-balanced by gender. The mean age in both vaccination groups was 69.4 years with 46 percent of the subjects at least 70 years of age and about 7 percent 80 years of age and older. And, as noted previously, the study population was largely caucasian.

The next two slides show the most common underlying medical conditions that were reported by subjects in the Adverse Event Monitoring Substudy, the Shingles Prevention Study. Of note, in a study this size, even a 1 percent incidence rate reflects enrollment of a fairly substantial number of patients with a given illness and these slides provide one measure of the heterogeneity of the population enrolled, this slide showing those conditions with an incidence rate of 5 percent or more and the following slide with the conditions that were seen in at least 1 percent of the subjects.

Embedded within the overall Shingles Prevention Study were a number of substudies. Among these were the Adverse Event Monitoring Substudy, a Cell-Mediated Immunity or CMI Substudy and a Persistence of Efficacy Substudy. The Adverse Event Monitoring Substudy, which was conducted at all 22 study sites, enrolled over 6,600 subjects who underwent a detailed assessment of local and systemic safety following vaccination.

The CMI Substudy, which was conducted at

only the Denver and San Diego sites, enrolled almost 1,400 individuals who had blood specimens obtained at baseline, at six weeks postvaccination and at subsequent time points.

The Persistence Substudy, which is still ongoing at 12 of the original 22 study sites, is following, approximately, 7,500 subjects who had been randomized to the vaccine group. The substudy is expected to provide information on the performance of the vaccine through, approximately, 10 years postvaccination and the findings of this substudy will be reported at a later date.

This is a pictorial representation of the study and substudy enrollment. Randomization was quite successful with nearly equal numbers randomized to vaccine and placebo in each of the age cohorts and, importantly, the study enrolled nearly as many subjects in the 70 plus age category as in the 60 to 69 age category.

The average duration of follow-up in the study was 3.1 years with a range of up to 4.9 years. Remarkably, only 0.6 percent of the subjects in each

vaccination group withdrew from the study or were lost to follow-up. This incredibly high degree of subject retention is a tribute to the effectiveness of the protocol-specified surveillance and the tremendous tenacity of the investigators and other study personnel at the 22 sites.

Over 95 percent of the subjects in each vaccination group remained in follow-up and conducted a closeout interview at the end of the study after accrual of all suspected herpes zoster cases was completed.

Shown here is an overview of the 42 day safety follow-up that was undertaken for all subjects enrolled in the study. More than 70 percent of the subjects either completed a vaccination report card if they were in the Adverse Event Monitoring Substudy or contacted the automated telephone response system, which was available to them for safety follow-up through day 51 postvaccination.

A variety of other types of subject contacts with the study sites were undertaken, including phone calls directly to and from sites, most

of them shortly after day 42. In all, about 97 percent of the subjects provided safety information following vaccination, including 93 percent establishing contact by day 60 postvaccination.

The active surveillance for suspected herpes zoster cases cast a very wide net. Through monthly contact with the automated telephone response system and/or the study sites, subjects with findings at all suggestive of herpes zoster were asked to report to the study site within 24 hours and if the investigator could not confirm an alternative diagnosis, the subject was entered into six months of protocol-specified follow-up.

The study sites performed an initial clinical evaluation and were reminded to use a low threshold for calling a rash illness a suspected case of herpes zoster. Lesion and blood samples were taken for laboratory analysis. The digital photographs were obtained. A number of shingles-specific questionnaires were administered in order to define the impact of the illness on the subject, and treatment with famciclovir and analgesics was

initiated.

And it's important to note that all of the enrolled subjects with suspected herpes zoster were urged to seek medical care immediately. These highly motivated subjects, well-educated about herpes zoster, received state of the art care by experts in the field with aggressive pain management and frequent, attentive follow-up by study personnel.

Thus, the vaccine's efficacy was not evaluated in the setting of a placebo group that received no treatment, but rather one that received optimal care for their episodes of herpes zoster and PHN. The study had three key efficacy endpoints, the incidence of herpes zoster, the incidence of PHN and the herpes zoster burden of illness or BOI. Subsequent slides will describe each of these endpoints further.

Pain throughout the period of follow-up was scored on a 0-to-10 scale using a validated instrument. The primary efficacy analyses were based on a modified intention-to-treat approach that excluded only those patients, subjects, who dropped

out of the study or developed a case of herpes zoster within the first 30 days postvaccination.

This modified approach was employed to ensure that the primary efficacy analyses did not include those vaccine-associated rashes, a primary safety concern in the early days postvaccination, nor those cases of herpes zoster that may have already been in the prodromal phase at the time of vaccination and before the immune response could be elicited.

Although I will be presenting the MITT analyses this morning, the analyses were also performed using a full intention-to-treat approach, as were a variety of sensitivity analyses with virtually identical results.

As mentioned earlier in the presentation, the state of scientific knowledge when the Shingles Prevention Study began indicated that vaccination could prevent, might prevent PHN and lessen zoster-associated pain, but there was no evidence that vaccination could prevent herpes zoster altogether. Thus, the study was designed with two co-primary endpoints related to this important issue of pain, the

herpes zoster pain burden of illness and the incidence of PHN.

Incidence of herpes zoster was considered a tertiary endpoint. Because of the age-associated increase in the incidence of PHN, the study was designed to enroll subjects beginning at age 60. Following publication of the second Ann Arvin Proof of Concept Study and prior to study unblinding, Merck and CBER agreed to the elevation of herpes zoster incidence to a key secondary endpoint with a prospectively designed and defined criterion for success.

Turning now to the endpoint definitions. Suspected herpes zoster was defined as any subject with a suggestive cutaneous eruption. These subjects were evaluated by the study physicians and underwent the six months of protocol-specified follow-up that I just mentioned to monitor the presence and the amount of pain and discomfort, development of PHN and the development of any other possible complications.

Although the study cast a very wide net to accrue the suspected cases of herpes zoster, in the

end the protocol utilized very strict definitions of herpes zoster and PHN.

All suspected herpes zoster cases were clinically adjudicated by a Clinical Evaluation Committee made up of five independent, that is non-Merck, members of the study's Executive Committee. The Clinical Evaluation Committee adjudicated the cases in a blinded fashion according to a detailed Standard Operating Procedure with all laboratory data redacted from the clinical summaries.

Final confirmation of the herpes zoster cases was determined by a hierarchical algorithm that considered the results of PCR of skin lesions, viral culture and the decision of the Clinical Evaluation Committee in that order and, in the end, a large majority had final determinations based on PCR results.

For the purposes of the primary analysis, PHN was defined as zoster-associated pain with a score of 3 or higher on a 0-to-10 scale that was present for at least 90 days following herpes zoster rash onset. During earlier validation of the pain questionnaire,

it was found that a pain score of 3 or higher was correlated with functional limitation on activities of daily living.

The co-primary endpoint, the herpes zoster burden of illness or BOI, was a composite endpoint that was designed to capture the entire burden of pain due to herpes zoster, a population measure that reflected the incidence, the severity and the duration of zoster-associated pain and discomfort over six months following onset.

This slide includes a graphic that shows a curve representing the pain scores over time for a hypothetical subject who developed herpes zoster. With time noted on the X axis and the 0-to-10 scale on the Y axis, an individual severity-by-duration score is thus generated and the BOI represents the scores of all subjects in a particular group.

For the BOI and the other efficacy endpoints, the primary analysis was performed on the entire MITT population. So for each subject who developed an episode of herpes zoster, a severity-by-duration score was calculated and an area under the

curve constructed.

Those subjects who did not develop herpes zoster during the study were included in the analysis. They were assumed, however, to have had no zoster-associated pain and, thus, were given a severity-by-duration score of zero.

Incidence and severity-by-duration are both important to describing the overall burden of herpes zoster on patients and the outcome measure needed to reflect both of these components. And to help the Committee get a better grasp of the concept of BOI, which is a bit abstract, the following three slides give hypothetical examples of the BOI in action and I would like to thank Dr. Oxman for providing these slides to me.

In the first example, the putative vaccine reduces the incidence of herpes zoster, but the severity of those cases that do occur in the vaccine group are no lower than the severity in the placebo group, and the reduction in the BOI for the vaccine group is reflected at the bottom of the slide to show the impact on incidence but not severity.

Conversely, here we show the vaccine reducing the severity of the individual herpes zoster episodes, but no impact at all on the incidence of the disease. And the reduction in BOI once again shows benefit from the vaccine. In this third example, the vaccine reduces both incidence and severity-by-duration. And as you will soon see, this third example most closely reflects the outcome of the Shingles Prevention Study.

Shown here is a flow diagram of the 1,308 suspected herpes zoster cases that were followed during the course of the study. Of these, 481 were in the ZOSTAVAX group and 827 in the placebo group. Of note, across the two vaccination groups, similar numbers of subjects were determined not to have herpes zoster, 156 in the vaccine group, 161 in the placebo group, about 0.8 percent of the total population in each group, a finding that reflects the comprehensive and unbiased nature of case accrual.

Of the 322 and 662 herpes zoster cases respectively in the full intention-to-treat analysis population, nearly all were included in the primary

modified intention-to-treat population and of these about 93 percent in each vaccination group were diagnosed by PCR, about 5 percent in each group by the Clinical Evaluation Committee and the remainder by viral culture.

This figure provides an overview of the key efficacy results from the study for the three main endpoints, herpes zoster incidence, PHN incidence and the herpes zoster burden of illness. The vertical line at 25 percent efficacy reflects the pre-specified minimum criterion for success that had been established for each of these endpoints in discussions between Merck and the FDA.

The blue bars reflect the vaccine efficacy that was observed in the study along with the 95 percent confidence intervals for each endpoint. The slide shows that for each of three endpoints, the efficacies exceeded substantially the minimum criterion established for the study's success.

The two key messages from these results are, one, that the vaccine was able to significantly reduce the incidence of herpes zoster among the

vaccine recipients and, two, there was a significant impact on the severity of the herpes zoster episodes. And I will go on to discuss each of these endpoints in turn.

First, for herpes zoster incidence, this slide shows a Kaplan-Meier plot for the cumulative incidence of herpes zoster over time by vaccination group. The X axis indicates time of follow-up and on the Y axis, the proportion of subjects developing herpes zoster. 315 herpes zoster cases occurred in the ZOSTAVAX group compared with 642 cases in the placebo group.

The curve demonstrates a vaccine effect soon after vaccination. The two curves continue to diverge throughout the entire follow-up period. But note that follow-up beyond four years is rather limited because only a small fraction of the overall study population was followed for four years or longer.

One can see here that the most common complications of acute herpes zoster occurred at a lower rate among ZOSTAVAX recipients than among

placebo recipients. The neurologic complications, as shown on this slide, exclude the acute neuritic pain.

Complications of sacral dermatome involvement include such findings as urinary retention or incontinence, constipation or rectal incontinence and across these categories, the vaccine reduced the frequency of complications by, approximately, 65 to 75 percent and the reduction in these complications reflects the vaccine's effect on severe cases of herpes zoster.

Shown here is another Kaplan-Meier plot for PHN incidence using the protocol definition of pain greater than or equal to 3 present 90 days or longer after herpes onset. There were 27 cases of PHN in the vaccine group and 80 in the placebo group. Supportive analyses using alternative time points to define PHN, 30, 60, 120, 182 days, showed generally similar results.

As was the case with the herpes zoster endpoint, the vaccine effect was demonstrated early and then throughout follow-up. And note again the relatively small proportion of subjects with follow-up

extending out to four years or longer.

I would like to turn now to the herpes zoster pain burden of illness. As noted earlier, the BOI includes both the incidence of herpes zoster and the severity-by-duration of zoster-associated pain.

The overall efficacy for this endpoint was 61 percent with the 95 percent confidence intervals as shown. The BOI efficacy that was demonstrated in the study reflects a combined effect of both of these components. The 51 percent reduction in the incidence of herpes zoster was already described. With respect to severity-by-duration scores among those subjects who developed herpes zoster there was a statistically significant 22 percent reduction in the scores among those in the vaccine group.

Now, to put a human face on this reduction, because again these scores are a bit abstract, the reduction from a mean of, approximately, 180 to 140 creates a 40 point difference, which reflects nearly a two week reduction in the duration of clinically significant pain at a level of 3 or a four day reduction in pain at the maximum level of 10,

the worst imaginable pain. This indicates a huge impact in preventing suffering over and above the vaccine's impact and reducing the incidence of herpes zoster.

This slide gives another perspective on the impact of ZOSTAVAX beyond its ability to prevent cases of herpes zoster. The slide shows a histogram with the subjects who had the highest severity-by-duration scores. The increasing scores are shown on the X axis, the number of the cases on the Y axis. And for the purposes of illustration in this exploratory analysis, the scores of 600 or higher are depicted.

To obtain a score of 600 or higher, the subject would have to have the maximum pain score of 10 for at least two months or a score of 3 to 4, that is clinically significant pain, every day throughout the entire six month follow-up period. So we're talking about very severe cases of PHN.

The slide overall shows that there were only 22 vaccine recipients of 600 or higher compared with 40 recipients and that's a 73 percent reduction.

And if one looks at the slide beginning from the right and working toward the left, you can see the very dramatic effect of the vaccine at the farthest end of the pain spectrum.

Among those vaccine recipients who went on to develop PHN, the vaccine effect was equally clear. In an exploratory analysis, including those subjects who developed PHN that was in the license application, it was found that through the end of the follow-up, there was a 57 percent reduction in the severity-by-duration scores among those who received ZOSTAVAX compared with those who received placebo. This statistically significant benefit again shows evidence of the substantial role that the vaccine can play even in subjects who ultimately go on to develop PHN.

As noted earlier, subject enrollment in the study was stratified by age and this slide displays the vaccine effect for the three main study endpoints stratified by age. For the herpes zoster endpoint, there was 64 percent efficacy in the younger cohort and 38 percent efficacy in the older cohort. Despite this difference across the two age strata,

vaccine efficacy for herpes zoster incidence remained substantial even for the older age group.

Importantly, since PHN frequency and pain severity increase with age, the vaccine efficacy for PHN was comparable across the two age strata as shown. In fact, among subjects with herpes zoster the vaccine reduced the risk of developing PHN by a statistically significant 38.5 percent, including 47 percent reduced incidence in the 70 and older age group.

Because the vaccine retains substantial efficacy for those subjects with more severe pain associated with a zoster episode, the overall effect on burden of illness was relatively well-preserved among the older age group. Although the point estimate for the burden of illness was a bit higher in the younger group, reflecting the effect on the incidence, there is wide overlap in the confidence intervals between the two age strata because of the benefits on severity-by-duration in the older group.

ZOSTAVAX also had an effect on the incidence of zoster-associated interference with activities of daily living. These analyses were based

on the mean of the responses to seven ADL-related questions on a validated questionnaire using a 0-to-10 scale. The vaccine reduced the overall interference with activities of daily living by 66 percent in the overall population.

This combined score for the overall population is sensitive to the incidence, severity and duration of interference, and so it was analogous in many respects to the burden of illness for the overall population.

The vaccine also led to a 55 percent reduction in moderate-to-severe interference with daily living. Now, this reduction was of course influenced by the reduction in the incidence of herpes zoster. So in a pre-specified analysis to determine the vaccine effect on ADL interference above and beyond the vaccine's effect on the reduction of herpes zoster incidence, a reduction of 8 percent was seen, which was not statistically significant.

The duration of the vaccine efficacy was alluded to briefly in the prior Kaplan-Meier curves for efficacy, and this slide presents the efficacy for

herpes zoster and PHN over 48 months of follow-up. After an initial decline in efficacy during the first year, the point estimates for efficacy remain relatively stable through 48 months postvaccination.

Now, the confidence intervals do get wider over time reflecting fewer subjects with long follow-up and few with clinical endpoints. So the interpretation at the later time points becomes limited. However, the follow-up for the longer term persistence of efficacy is currently being evaluated, as previously noted, at 12 of the 22 sites and so additional information will be accruing over time.

Thus, the Shingles Prevention Study has shown conclusively that vaccination can reduce the incidence of herpes zoster with better efficacy among the younger age cohort, reduce the incidence of PHN and reduce the burden of illness associated with herpes zoster pain.

For the pain-related endpoints, the vaccine efficacy was very well-maintained in the older cohort compared with the younger cohort. The vaccine also reduced the duration of pain and the risk of

substantial interference with activities of daily living and, thus far, the efficacy has extended out to four years.

I would like to turn now to the immunogenicity results. Declining VZV-specific immunity most frequently associated with age is thought to be a precursor for the development of herpes zoster and, as such, the immune response to vaccination is thought to be reflected in efficacy.

The ZOSTAVAX clinical studies evaluated immune responses using two key validated assays of VZV-specific interferon-gamma enzyme-linked immunospot assay and a glycoprotein enzyme-linked immunosorbent assay that has been used to measure antibody responses in the varicella vaccine programs for many years. The VZV-specific antibody measured through the gpELISA is known to be T-cell dependent and is, therefore, felt to reflect the cellular immune response to vaccination.

In the pivotal efficacy study, the primary endpoints for immunogenicity by these assays and also for the responder cell frequency assay were assessed

at six weeks postvaccination. And on the next few slides, these endpoints, the endpoints that will be shown, are the ratio of the geometric mean titers or counts in the vaccine and placebo groups, as well as the geometric mean fold increases from baseline.

At six weeks postvaccination in the Shingles Prevention Study, immune responses were seen for both of the key validated assays. Of note, of course, these are previously VZV experienced individuals and so even at baseline, rather high levels of preexisting VZV immunity were seen. And, as you can see, relative to the day zero levels, the VZV antibody measured by gpELISA increased 1.7-fold and the ELISPOT counts increased 2.0-fold, both of which were statistically significant increases.

In a regression model that looked at each of these immune markers as possible correlates for prevention of herpes zoster, both the gpELISA and the VZV interferon-gamma ELISPOT assay correlated with protection. However, the gpELISA correlated best with efficacy, as shown in the slide, with each log unit increase associated with a larger risk reduction.

Note importantly that this is a correlation for values across the population. No specific value in either assay can reliably predict whether an individual subject is protected from herpes zoster, and so the study was unfortunately unable to define a true surrogate.

Looking at the different age cohorts, one sees immune responses that are generally similar with slightly higher geometric mean fold rises from baseline and postvaccination geometric mean titers for the younger group. Immunogenicity in adults has been evaluated in the VARIVAX and ZOSTAVAX Program, including both seronegative and seropositive individuals, and the vaccine has been shown to be immunogenic in adults.

To lend further support to the utility of the vaccine, this slide provides a preliminary summary from a subset of subjects who were enrolled in a recently completed study that was not included in the original license application. And with all studies that have been initiated since 2003, this protocol, Protocol 010, enrolled subjects beginning at age 50.

The slide shows preliminary results for 113 subjects, 45 of whom are 50 to 59 years of age, 68 of whom are 60 to 69 years of age or, I'm sorry, 60 years of age or older. Note that in this study the postvaccination blood sample was obtained at four weeks postvaccination. Not surprisingly, the immune responses in the 50 to 59 group were as good as those in the 60 and older group.

So in summary, in the face of often high levels of preexisting immunity, ZOSTAVAX elicits an immune response by both gpELISA and ELISPOT. The VZV antibody response measured by gpELISA, a T-dependent phenomenon that reflects cellular immunity, correlates best among the assays evaluated with protection against herpes zoster.

I would like to move on now to the safety profile of the vaccine. It's important to remember that ZOSTAVAX is a high potency Oka/Merck VZV vaccine that builds on an extensive VARIVAX safety database. More than 56 million doses of VARIVAX have been distributed mostly in VZV naive individuals since the initial licensure of the product in 1995. VARIVAX has

demonstrated an excellent safety profile in the ensuing ten years.

Within the ZOSTAVAX Program, the clinical evaluation includes over 20,000 subjects who receive vaccine and importantly over 19,000 placebo controls. So this assessment of safety was performed in a rigorous comparative setting that permitted a reliable enumeration of both common and uncommon adverse experiences. As shown here, the studies that were conducted had 97.5 power to detect an event with a rate of 1.8 per 10,000 and 80 percent power to detect an event with a rate of 0.8 per 10,000. The studies have demonstrated that ZOSTAVAX was generally well-tolerated in these older adults.

With regard to the safety evaluation in the Shingles Prevention Study, the following safety evaluation was undertaken for all enrolled subjects. Adverse experiences occurring day 0 to 42 were to be reported and assessed. Vaccine-related serious adverse experiences occurring at any time during the study were also to be reported, as were deaths at any time following vaccination.

As previously noted, all subjects enrolled in the study were to have contact shortly after day 42 postvaccination to ensure complete ascertainment of serious adverse experiences in the full cohort and 93 percent of them did by day 60 and 97 percent overall. The Adverse Event Monitoring Substudy again conducted at all of the sites and including over 6,600 subjects added two additional measures over and above the safety evaluation that was done for the overall population in the Routine Safety Cohort.

In addition to the standard safety evaluation that was on the prior slide, the subjects completed a diary, a vaccination report card through day 42 postvaccination. And in addition for this cohort, hospitalizations for any cause were to be reported through the end of the study. For the overall study population, the incidence of serious adverse experiences in each vaccination group was identical with a rate of under 1.4 percent.

In the Adverse Event Monitoring Substudy shown in the hash marks here, more serious adverse experiences were reported in the ZOSTAVAX group than

in the placebo group, which was offset by a corresponding increase in the serious adverse experiences reported among placebo recipients in the Routine Safety Cohort.

Now, this table reflects the distribution of serious adverse experiences in the two safety cohorts. A review of the serious adverse experiences in the substudy found that no body system, no clinical syndrome, no diagnosis was responsible for this difference and there was no temporal clustering of these serious adverse experiences relative to vaccination.

Given the follow-up for and distribution of these serious adverse experiences in the overall population, the conclusion of the detailed review was that the imbalance and serious adverse experiences in the substudy was chance event. In further support of the safety profile of the vaccine, in the entire cohort of nearly 40,000 vaccinated subjects, there was a total of only five possibly vaccine-related serious adverse experiences reported. Two in the vaccine group and three in the placebo group. The number of

deaths during both the first 42 days postvaccination as well as during the entire study were the same in the two vaccination groups and there were no vaccine-related discontinuations at all in the study.

In the Adverse Event Monitoring Substudy, the data recorded in the vaccination report cards demonstrated, not unexpectedly, that injection-site adverse experiences were more frequent in the ZOSTAVAX group than in the placebo group. The recording of intensity demonstrated that most of these, approximately, 85 percent were scored as mild by the subjects.

In this double-blind experience, the overall proportion of subjects with systemic clinical adverse experiences was the same in both groups, just under a quarter. An increase in vaccine-related systemic adverse experiences was observed in the vaccine group, but the rates in both the vaccine and placebo groups were low, about 6 percent in the ZOSTAVAX group and about 5 percent in the placebo group.

Among the vaccine-related adverse

experiences only headache was seen more frequently in the vaccine group than in the placebo group. Hospitalization rates at any time during the study for any reason were comparable at 107 per 1,000 person-years.

I would like to turn now to Protocol 009, the safety study that was conducted at the estimated maximum vaccine potency. This double-blind controlled multicenter trial, which enrolled subjects 50 years of age and older, evaluated two lots of the vaccine that were administered at 58,000 and 207,000 plaque-forming units per dose. About 700 subjects were enrolled with nearly 200 of them 50 to 59 years of age. The vaccine was generally well-tolerated at both potencies as shown in the next slide.

Here we have the overall safety findings of the study by potency group and age cohort. The proportion of subjects with local adverse experiences was higher at the higher potency and the younger age cohort reported these local reactions more often than the older cohort, but these events were viewed almost exclusively as mild or moderate in intensity and of

relatively brief duration of just a few days.

Importantly, the frequency of systemic adverse experiences was similar in the higher and lower potency groups and overall the vaccine was generally well-tolerated at both of the potencies administered. A relatively small number of VZV-seronegative adults has been identified and enrolled through our clinical trials. No seronegatives at all were seen among the 1,400 subjects in the CMI Substudy of the Shingles Prevention Study.

A different study, Protocol 003, was conducted in tropical countries specifically to enhance the potential for identifying VZV-seronegative adults, because published literature suggests that VZV-seroprevalence is lower and seropositivity obtained at a later age than in temperate climates. Despite screening over 1,100 individuals, few VZV-seronegative adults were found and enrolled.

In Protocol 049, from the VARIVAX Program, varicella history negative adolescents and adults were enrolled. Among these, 17 VZV-seronegative subjects 30 years of age and older were identified. In this

small subset from the two studies, it appears that local and systemic adverse experiences as well as elevated temperatures occurred frequencies that are similar to those seen in VZV experienced individuals.

Importantly though, despite concerted efforts to identify such individuals, VZV-seronegativity is very rare among persons over the age of 30. Based on these findings, the criteria for enrollment in the ZOSTAVAX studies which did not screen for VZV-serostatus, there is no need to screen or otherwise assess pre-vaccination immune status in individuals who are otherwise candidates for ZOSTAVAX.

An adverse experience of particular interest in the ZOSTAVAX Program, as it has been in all of the varicella vaccine programs, was the development of rash within 42 days after vaccination. In that time frame, within ZOSTAVAX clinical trials, approximately, 0.3 percent of subjects reported a VZV-like rash across the database. A rate that is roughly 10-fold lower than that seen following administration of VARIVAX.

Those who developed VZV-like rash were

requested to have sample lesions obtained for PCR analysis. Across the entire clinical database, two subjects with VZV-like rash were found to have the Oka vaccine strain in their lesions. Among the subjects in the Shingles Prevention Study, the Oka/Merck strain was not identified in any suspected herpes zoster case or in any postvaccination rash at any time point early or late in the postvaccination period.

So in summary, compared with placebo those who received ZOSTAVAX had a higher incidence of injection-site reactions, but a similar overall incidence of systemic clinical adverse experiences. The incidence of vaccine-related and systemic experiences was slightly higher among ZOSTAVAX recipients than among placebo recipients. Following a dose of ZOSTAVAX vaccine-associated rashes were uncommon and so we conclude that overall the vaccine had a very acceptable safety profile in those 50 years of age and older.

So to summarize, ZOSTAVAX is proposed for vaccination of individuals beginning at 50 years of age. Although the pivotal efficacy study enrolled

subjects beginning at 60 years of age, the epidemiological data and the limitations of currently available therapies argue that there is a strong medical need to prevent herpes zoster and its complications starting at age 50.

Over 100,000 additional cases of herpes zoster and an additional 8,000 to 15,000 additional cases of PHN could be potentially prevented each year in a group of individuals who suffer as much acute zoster-associated pain as those 60 to 69 years of age. With the additional societal burden of being an age group in which a majority of the population is still employed, the data indicates that substantial benefit could accrue from vaccination beginning at age 50.

Efficacy for ZOSTAVAX had been demonstrated directly for those 60 years of age and older with a very high degree of efficacy against herpes zoster, 64 percent, among those 60 to 69 years of age. Efficacy in this age group should predict well the efficacy in persons 50 to 59 years of age. The vaccine has been shown to be immunogenic with generally comparable responses in the 60 to 69 and 70

plus cohorts in the Shingles Prevention Study.

Similar age-related findings were observed in other ZOSTAVAX studies. Most recently in the form of the supportive data that have recently become available from Protocol 010 for those 50 to 59 years of age. The vaccine has been administered in clinical studies to individuals 50 years of age and older and has been shown to be well-tolerated with only a moderate increase in transient injection-site reactions of mild to moderate intensity.

To conclude, in a very large clinical database ZOSTAVAX has been shown to reduce herpes zoster by one-half, reduce PHN by two-thirds and to reduce herpes zoster pain burden of illness by over 60 percent in older adults. The vaccine elicits a VZV-specific immune response, demonstrates efficacy that persists for four years postvaccination and has an excellent safety profile.

At this point, I would like to turn the podium back to Dr. Gutsch for a few concluding remarks.

DR. GUTSCH: In addition to the large and

comprehensive database that went into the application for licensure, there are ongoing and future plans for further study of ZOSTAVAX that will shed light onto the vaccine performance. To answer the question what is the durability of ZOSTAVAX efficacy? There is continuation of the Shingles Prevention Study at 12 of the 22 original sites involving 7,500 subjects.

In addition, up to 18,000 of the placebo recipients in the Shingles Prevention Study and Protocol 007 are in the process of receiving vaccination with ZOSTAVAX and this will then provide further safety follow-up.

A clinical study is being conducted to assess a new formulation of ZOSTAVAX that allows refrigerator storage to increase the settings in which the vaccine will be available. Another study is being conducted to show that ZOSTAVAX can be administered concomitantly with inactivated influenza vaccine. Pharmacovigilance planning is important for a vaccine as it enters the postmarketing period.

A pharmacovigilance plan was developed that builds on the extensive VARIVAX experience with

over 56 million doses distributed to the market and ZOSTAVAX for which a robust database has been provided in a licensed application. Proposed plans include extension of the postmarketing surveillance activities that are well-established at Merck for vaccines to monitor adverse events after licensure.

In addition, the VZV Identification Program determines by a preliminary chain reaction if wild type or vaccine strain, varicella zoster virus, is present in clinical specimens, such as vesicle fluid or cerebral spinal fluid from individuals with adverse experiences.

Finally, the Pregnancy Registry that was initiated with the VARIVAX Program in 1995 will also be applied to ZOSTAVAX in the postmarketing period. Collectively, results from our program indicate that the benefit/risk ratio for ZOSTAVAX is favorable. Herpes zoster and PHN are often debilitating diseases in need of better management. ZOSTAVAX would be the first intervention when licensed to prevent herpes zoster and its complications, including postherpetic neuralgia.

Beyond the benefit from preventing these two diseases, ZOSTAVAX also reduces the severe pain associated with herpes zoster and PHN. ZOSTAVAX has been studied in subjects 50 years of age and older and has demonstrated an excellent safety profile with no clinically important safety risks identified from a very large database of placebo-controlled clinical trials. So overall, the benefit/risk ratio is favorable and ZOSTAVAX, when licensed, will meet an important unmet medical need.

In closing, the proposed indications for ZOSTAVAX supported by the clinical data just presented are: ZOSTAVAX is indicated for prevention of herpes zoster, prevention of PHN, reduction of acute and chronic zoster-associated pain. ZOSTAVAX is indicated for immunization of individuals 50 years of age and older. Thank you very much. We can now entertain your questions.

CHAIRMAN OVERTURF: Are there questions from the Committee for the sponsors at this time? Dr. Wharton?

DR. WHARTON: I have a couple of questions

about safety monitoring. I'm a little confused about the group who were in the safety substudy. Did they participate in the 42 day automated telephone call? From the first slide it seemed as if they didn't and then later it was stated that the supplemental safety monitoring was on top of other safety monitoring being done.

DR. SILBER: The question relates to the type of safety follow-up for the subjects in the Adverse Event Monitoring Substudy. And as initially designed, all subjects were to have the day 42 contact by phone or through other contact with the sites. And the vaccination report card was used for that subset of 6,600 individuals. It became apparent through frequent phone calls to the sites that the subjects found it a bit of an annoyance to have to go through all of this redundancy having already completed a 42 day diary card, so that the protocol through an operations memorandum permitted either of those contacts to be a suitable completion of the 42 day contact.

So the majority of those subjects who were

enrolled in the Safety Monitoring Substudy had the vaccination report card in lieu of the phone call. But for those who didn't turn in the vaccination report card or for some who did both, there may have been, and actually in other respects, more than one form of contact. In the pie chart that was shown any given subject was only counted once with the vaccination report card and the ATRS being prioritized.

DR. WHARTON: Okay. And I want to follow-up to that. For the subjects who didn't have contact with the investigators within 60 days of vaccination, which I think were about 7 percent on your pie chart, when was information on those subjects attained and how was it obtained?

DR. SILBER: Yes, that was variable. First, I should say for the persons who were involved in the Adverse Event Monitoring Substudy, about 97 percent returned those vaccination report cards. For the remaining individuals, the small subset who had follow-up beyond the day 60, it was highly variable. Many of those were in contact by day 90, but some went

on longer.

I recall that after this initial follow-up period for safety, the monthly contacts for efficacy were continuing and so there were reminders to the subjects on a monthly basis. Despite all of these efforts and despite the very careful attention to follow-up for efficacy and safety by the investigators, we still had 3 percent who ultimately had no follow-up for safety.

CHAIRMAN OVERTURF: Dr. Hetherington?

DR. HETHERINGTON: How are the patients in the Safety Substudy selected and recruited and how do they compare to the general population in the study?

DR. SILBER: Yes, thank you. That's a question about the selection of subjects in the AE Substudy. What happened was, as you can imagine, this was a very huge endeavor to undertake to have a study of this size at 22 sites. And the way that the Adverse Event Monitoring Substudy was conducted was that basically after the first several months that allowed the sites to sort of settle in with their procedures and do the routine activities, each of the

sites was then asked to consecutively recruit the next 300 individuals into the Adverse Event Monitoring Substudy.

And so there was no cherry picking or preselection that happened. And then at the time when that cohort was filled, the routine cohort continued. And so that through the randomization and through the way that the timing intervals occurred, there were no differences, overall differences demographically or in other ways between the two cohorts.

DR. HETHERINGTON: Did the patients have a -- were they able to elect whether to participate or not? Could they decline the long-term or the Safety Substudy participation? And if so, what was the rate?

DR. SILBER: I believe I'm going to have to turn to Dr. Levin for confirmation. But my understanding is that subjects could opt out of the Adverse Event Monitoring Substudy and remain in the routine cohort, but the communications that I have heard from Dr. Oxman and Dr. Levin and others over the years is that it was a very small number who did so.

DR. HETHERINGTON: Could we get that exact

number some time this morning?

DR. SILBER: We will certainly try.

DR. HETHERINGTON: And did you ever compare the demographics and the age distribution in that subgroup versus the general population?

DR. SILBER: They were similar.

CHAIRMAN OVERTURF: Dr. Farley?

MEMBER FARLEY: I have some questions about what is known about the more detail of the epidemiology in the 50 to 59 year-old group that has sort of been added into this expanded request. And do you know whether those who develop herpes zoster in that decade are more likely to be immunocompromised, more likely to be HIV with reconstitution syndromes or people on steroids or with malignancies and therefore might not be in the targeted group, at least initially for this vaccine?

And also, do you know anything about the epidemiology of zoster in the last decade of general use of the varicella vaccine? Has that had an impact not having natural chicken pox out there as much by far as previously and in terms of if there is a

boosting effect of exposure as adults?

And finally, do you have any information about the durability of the immune response that you showed us the small numbers of 50 to 59 year-olds, because, of course, the issue will be will they not have the benefit when they are at maximum risk later?

DR. SILBER: Okay. So there were at least three questions there, so I'll try to take each of them. I'll start with the VARIVAX question and influence of varicella vaccination on the incidence of herpes zoster. In fact, the few population-based databases that have been available long-term suggested the incidence of herpes zoster has been increasing for at least the last 50 years. Both in terms of absolute numbers and in terms of age adjustment.

The data that are available thus far, realize are only 10 years out from onset of varicella vaccination and only about seven years out from widespread use of the vaccine. And so it may be too early to see anything, but the fact is that the studies that have been completed to date, some of them at CDC, at Group Health Cooperative out in Seattle

have indicated that thus far there does not appear to be any differences in the incidence of herpes zoster with the use of varicella vaccine.

Now, there are mathematical models that have predicted that this will happen over time and that with less boosting from exogenous exposure, assuming that there is not endogenous boosting to make up for that, that the incidence of herpes zoster may increase. And, in fact, that the age of zoster may shift to an earlier age. But, at this point, it remains speculative and the available data do not indicate that this is happening as yet.

With respect to the demographics and characteristics of persons 50 to 59 years-old who develop herpes zoster, the fact is that the population has a higher percentage of immunocompromised with age. And so in terms of the overall population, there were fewer immunocompromised individuals in their 50s than in their 60s, 70s and later. There are few data looking specifically at immune status in the 50 to 59s, but such that is available suggests that the large majority of the cases of herpes zoster among

people in their 50s are in the immune-competent population.

Your third question had to do with the durability of the immune response and the durability of protection that would ensue. And what we have seen with vaccination in terms of the CMI Substudy that went out to three years and also following an episode of herpes zoster actually, that there is an early and large increase, but that within six months the markers of immunity tend to decline and head back toward baseline, as one might expect even with silent exogenous or endogenous boosting.

And it appears that following an episode of zoster and following vaccination, people sort of settle out at a level and this is what one might expect when we are dealing with a memory response in the face of prior immunity. And so in terms of the actual immunologic markers, they do head back toward, but still remain above the baseline values. However, in terms of the vaccine efficacy, as one looks at year two, year three, year four, there was no decline seen in the point estimates for efficacy.

So at least from the clinical protection standpoint, even for those 60 and older, a decline in durability has not yet been observed. And one would expect that vaccination of an even younger adult cohort 50 to 59 durability would be at least as good as is seen with other vaccines.

CHAIRMAN OVERTURF: Dr. Markovitz?

MEMBER MARKOVITZ: Yes, I have two questions. The first one is in terms of safety in the 50 to 59 year-old group, unless I missed it, the only slide we saw was with these higher doses. And of course, there is a lot of reactogenicity, you know, systemic reactions around 40 percent in all age groups. But yet, it is stated that the vaccine was "well-tolerated." Can we have some elaboration on that? And then I have a second question.

DR. SILBER: Sure. If we can pull up the safety table?

MEMBER MARKOVITZ: 74.

DR. SILBER: Across the ZOSTAVAX Clinical Development Program, most of the studies were placebo-controlled. And as you might recall from the Adverse

Event Monitoring Substudy in the Shingles Prevention Study, roughly a quarter of those individuals receiving placebo had one or more systemic adverse experiences. And so just to sort of put a frame of reference around it, that's what is seen after placebo injection.

And across ZOSTAVAX studies, we tend to see systemic adverse experience rates in this range. And as you see, we can look at it both ways across the potencies horizontally across the age groups vertically. There was really not a large difference across the potencies. In fact, in the younger age cohort, the rate of reporting of systemic adverse experiences was actually lower in the higher potency than it was in the lower potency.

And in this study the reporting rate was within a couple of percentage points of those for the 60 plus. And again, other than a slightly higher incidence of headache in the younger group, there were no differences seen by body system, by clinical syndrome, by any other diagnostic criteria and a very small percentage of any of these adverse experiences

were rated as severe in intensity by the subjects.

CHAIRMAN OVERTURF: Just a point of clarification before Dr. Markovitz asks the second question. Both the higher and the lower potency dose in the 50 to 59 year-old age group are considerably higher than the overall dose that you are asking for approval. Is that correct or am I confused on that issue?

DR. SILBER: I'm sorry, the potencies administered?

CHAIRMAN OVERTURF: Yes, the potencies.

DR. SILBER: Is that what you are asking? Yes, the question is about the potencies administered here. The lower potency within Protocol 009 was 58,000 plaque-forming units and doses of around 50,000 plaque-forming units were the highest potencies administered within the Shingles Prevention Study, which had 12 different lots, and 50,000 was also the potency that was administered in several of the other clinical studies.

And so we selected a lower potency within this study really to help us benchmark to the other

studies, because we didn't have a placebo control here. And prior to Protocol 009, the highest potency we administered in any prior clinical trial was 67,000 plaque-forming units, and so the higher potency group here was about a 3-fold higher potency that had been administered previously. And we don't expect that very many people would ever receive a potency this high out in clinical practice.

CHAIRMAN OVERTURF: In fact, I was wondering --

PARTICIPANT: I don't think that answered the Chair's question. The Chair asked a very important question here and I just --

CHAIRMAN OVERTURF: Yes. To me what you're asking for is approval of licensure for the 50 to 59 year-old age group, but you're asking for approval for a dose that is considerably lower than either one of these. Is that correct?

DR. SILBER: Well, the specification for this, as for other live virus products, is built around a minimum expiry, a minimum potency that would be observed at expiry and so the clinical experience

from the time the vaccine is manufactured and released would be at a variety of potencies higher than that, and so there would be a spectrum of potencies administered.

And so much as the Shingles Prevention Study evaluated efficacy at the lowest, largely at the lowest potency, so we are looking at safety at the highest potency to provide a buffer, if you will, for what might be seen in terms of the efficacy experience on the one hand and the safety experience on the other hand when a vaccine might be administered in practice. Did that answer it not?

CHAIRMAN OVERTURF: We may come back to this issue, but let Dr. Markovitz ask.

MEMBER MARKOVITZ: Yes. Actually, that's what I was trying to get to also because, essentially, most of the data you showed us for the older people, meaning 60 and over, were based on I believe a 19,000, was it, plaque-forming unit dose and here it's much higher.

So I guess what I'm really asking or suggesting is you have no data that deals with the

actual vaccine going into 50 year-olds in terms of safety, is that right, or you haven't presented it?

DR. SILBER: No, this -- I'll take a step back on this. The Shingles Prevention Study included 12 lots of vaccine that ranged in potency from roughly 20,000 plaque-forming units up to roughly 60,000 plaque-forming units. The dossier included a number of other studies, including but not limited to Protocol 009, that also used vaccine at a range of potencies up to 67,000 plaque-forming units.

Across that dose range, let's take it separate from Protocol 009 for a moment, across the dose range seen and actually reflecting what has been seen for many years with VARIVAX across a wide range of potencies for seronegative individuals is that other than a potency-related increase in injection-site reactions, no difference was seen in the safety profile.

So that is what was seen for all of these other studies and, in fact, the dose selection studies prior to the Shingles Prevention Study were looking at whether there was any dose-related effect.

Jump now to Protocol 009 and, again, to create the highest hurdle, if you will, for safety because it is at the maximum potency that someone might expect, this is what was seen. And, again, with systemic safety consistent with what was seen in other trials with local reactions at a somewhat higher reporting rate.

MEMBER MARKOVITZ: But these other protocols actually dealt with 50 to 59 year-olds before, too?

DR. SILBER: No. The shingles?

MEMBER MARKOVITZ: When you talk about that you tested a wide range of doses of the vaccine, what I'm trying to understand is what percentage of those people who got vaccine, what's in the range of what is going to actually go into people in a clinical setting, were in the 50 to 59 year-old range?

DR. SILBER: Right. The data that were included in the original dossier included, approximately, 200 to 300 subjects, most of them from Protocol 009, some of them from Protocol 049 that was alluded to, which was actually a VARIVAX protocol but

included what for VARIVAX is a high potency lot that was actually used in the Shingles Prevention Study at, approximately, 50,000 plaque-forming units also.

And so in terms of the database within the dossier, again because enrollment starting at age 50 only began in the studies in 2003, that is what is in the dossier. The studies that have been conducted since, including the Refrigerated Vaccine Bridging Study and the Influenza Concomitant Use Study, both of which are at or near completion, also included the vaccination of individuals beginning at age 50 and has gone through a range of safety doses.

And, again, younger individuals in general seem to report adverse experiences more often than the elderly. And so with this population and with the highest maximum potency, we consider that the data here provide comfort that vaccine administered at lower potency than that maximum would be with an acceptable safety profile for the age group.

MEMBER MARKOVITZ: What will be the actual dose of the vaccine going into people in a clinical setting if license is granted?

DR. SILBER: Do you want to answer that one? I think I will turn to Dr. Gutsch for a moment to answer that.

DR. GUTSCH: Just for clarification, this is a live virus vaccine so there is a shelf life during which the vaccine has a decaying potency that occurs over time just due to storage conditions. And so there is not one dose that anyone is going to get at any given time.

What we want to assure is that at the expiry potency, the potency at the very end, that it never goes below that so that we have an efficacious vaccine. But we have to put sufficient virus in there of this live virus to ensure that at the end of this shelf life, there is sufficient left over. And in order to do that we need a little bit of a range there and, therefore, we test the lower extreme for efficacy and the upper extreme for safety.

So we can't really say that you're going to get one specific dose, but the label indicates that you will get greater than 19,400 plaque-forming units. Does that clarify things?

MEMBER MARKOVITZ: Yes, thanks, that does.

CHAIRMAN OVERTURF: Dr. Karron?

MEMBER KARRON: So I have three sets of questions, one related to dose and potency, one related to safety and then finally to the gpELISA. So, first, I just wanted to know in terms of understanding about dose, actually really two sets of questions, one to follow-up on Dr. Markovitz'.

So in the VA study, were there multiple lots of vaccine used and were they of different potencies? And in terms of looking at efficacy, did you stratify by potencies to see if there was any difference in efficacy according to potency of vaccine?

DR. SILBER: Shall I answer that one first?

MEMBER KARRON: Yes, yes.

DR. SILBER: Okay. The question had to do with the lots that were used in the Shingles Prevention Study. In all there were 12 lots that were used, as I mentioned previously, at release potencies ranging from 20 some odd thousand up to about 60,000

with doses administered going from about 18,700 up to close to 60,000.

Included within those 12 lots was a three lot consistency series. What we found, what was found across the lots and across the potencies, and the trial was not powered based on the efficacy endpoints to demonstrate formally consistency, but when one looks at the lots by potency across the 12 lots and, in particular, when one does a comparison pair-wise within the three consistency lots, in both cases there were no differences observed with respect to efficacy for any of the three endpoints and with the potencies.

MEMBER KARRON: Okay. And then to follow-up on that issue, when the original studies, the dose ranging studies, were done to choose a dose to go forward with, had you done that looking over an age range?

Did you look at the young elderly and the very elderly in terms of making that decision?

DR. SILBER: Yes. The early dose selection studies that included the immunogenicity assessment were done in individuals 60 years of age

and older. There were a couple of earlier pilot studies that enrolled people beginning at 55, but Protocols 001 and 002, which were the ones that were alluded to in the Clinical Development Program overview slide that I gave, included individuals 60 years of age and older.

At that point, the interferon-gamma ELISPOT assay was not operative. There were a number of cytokine ELISAs, the responder cell frequency. A number of candidate markers were used with slightly different patterns in terms of when immunity developed, but across the assays that were being used at that time it was in the range of 17,000, 19,000 for two of the potencies that we did administer that we started to reliably see across the different markers that there was an immune response.

MEMBER KARRON: Okay. And I just want to understand better the rationale for the high dose study in the younger individuals, so somewhere between 5 and 10 times the dose, the minimum dose, the minimum 19,000 PFU dose.

I mean, is that because there are

potentially future plans to try to have a higher potency vaccine? What was the rationale for that higher dose?

DR. SILBER: The question surrounding the rationale for Protocol 009 was really just to frame at the very highest end of what might be manufactured, because the manufacturing will be targeted, again, to ensure that all doses administered within human certainty will be above a certain minimum potency, that there will be a target and variable potencies, as Dr. Gutsch had alluded.

And, again, this is really just to frame what could be acceptable at the very high range. If you're asking if we're specifically targeting 200,000 plaque-forming units as a dose for this or future studies, the answer is no.

MEMBER KARRON: Okay. Okay. So those were my potency questions. Safety questions. I was actually wondering if we could look at that slide 36 again, which is the pie diagram? I don't know if it's possible to pull up.

DR. SILBER: Sure. Can we get 36? Thank

you.

MEMBER KARRON: Okay. So I think if I understood the briefing documents correctly -- so, first of all, I want to clarify. The blue are the individuals in the detailed Safety Substudy?

DR. SILBER: That is correct.

MEMBER KARRON: Is that right? Okay. If I read the pie, the briefing documents, correctly, I think that there are about 25 percent of the people in this large study for whom I would say that safety data collection was not absolutely optimal. It was after day 42. In some cases is was well after that time. It had to be sort of sought by study personnel and such.

And my question is for those people not in the blue and the green --

DR. SILBER: Sure.

MEMBER KARRON: And I would sort of like detailed information about this. Are they comparable in terms of age, in terms of underlying conditions, in terms of whatever demographics we can measure to the people in the blue and green?

DR. SILBER: Sure.

MEMBER KARRON: Whom I do think we have good safety data on.

DR. SILBER: Okay. So the question has to do with the characteristics of those people who had other than an ATRS contact by day 50, other than a vaccination report card.

Before answering that, I would just like to turn attention to particularly this magenta or purple and gray. These two bars or two pieces of the pie represent over 20 percent of the individuals in each group, and these represent either the staff calling ATRS, basically on behalf of the subject, due to some contact or the staff following up on an ATRS fax, because again at day 50 or 51 it is shut down.

And just as with the vaccination report cards, not everybody comes in exactly on day 42. It might be sometime later. Out of these 21, 22 percent of individuals in the gray bars, the timing of when those contacts took place is known and roughly 80 to 90 percent of those additional subjects also had that contact prior to day 60.

So it could have been for any number of reasons. Without going to the ATRS, a subject may have called the site directly to say, hey, I had this really bad sore arm or, hey, I remember that I was supposed to check in six weeks later and I'm calling you or I have this rash, maybe it's shingles, can I come in? There are going to be all different ways in which this sort of contact might have occurred, and so been done in lieu of the green or the blue.

So having said that, I don't have at my fingertips any of the demographics or the characteristics of the persons in the bars, in the pieces other than green or blue, but we could check on that.

MEMBER KARRON: I think that would be very helpful. My last question actually just has to do with the gpELISA and the comment that that's the best correlate protection. And my question is really so when we look at responses in the sort of younger, the under 70s and the older 70s, in fact, over 70s have higher titers.

So what my question is is so does it

correlate best, say, with protection against postherpetic neuralgia or burden of illness as opposed to incidence because, in fact, the incidence efficacy is much less in the over 70 group?

DR. SILBER: Sure, yes. The question has to do with the surrogacy of or, I'm sorry, the correlation, there is no surrogacy, the correlation of the gpELISA.

Now, recall that these assays were conducted just on the CMI Substudy representing 1,400 of the 38,000 individuals enrolled in the study. And so there were relatively few clinical endpoints among the primary efficacy endpoints that occurred among the individuals within the substudy. Unfortunately, there was no blood collected from the other 37,000.

And so based on that, and I can't recall, I think there were only one or two or just a handful of PHNs at all across either of the treatment groups within the substudy. So the analysis looking at the correlation with protection was built on the protection against the incidence of herpes zoster.

CHAIRMAN OVERTURF: Dr. Fleming?

DR. FLEMING: I'm trying to pare down questions here. There are three areas of questions I would like to pursue, the first relating to generalizability, the second relating to safety, the third relating to the BOI for efficacy.

Starting on generalizability, your label is very broad. You're asking in slide 5 for immunization of individuals over age 50 and then note in the EpiData that the only known risk factors are age and immunosuppression. And, yet, you completely excluded patients, for example, that were on regular use of inhaled corticosteroids.

You have also excluded other high risk patients, patients that are homebound or non-ambulatory or have cognitive impairment and your representation of those patients over the age of 80 is only 2,500, a very small fraction, a fraction that in fact shows very little efficacy when you look at the age relationship to efficacy, and a group that shows on slide 71 to have a particularly higher excess rate of SAEs.

So the first of the generalizability

questions is why such an under-representation of those very groups that your risk factor analysis says are the people in greatest need?

DR. SILBER: Okay. That was a dense question. Can I answer that one before any other questions? Okay. The clinical studies for ZOSTAVAX, as for the other live virus vaccines, have routinely systematically included or excluded, excuse me, those with known immunosuppression.

And so with respect to generalizability, the studies were conducted in this way and the proposed package circular that has been submitted would contraindicate the vaccine in those with known immunodeficiency, as is consistent with a label as it had been for VARIVAX. And particularly because of the high potencies administered, there were potential safety concerns with using a high potency vaccine in individuals with known immunodeficiency.

Having said that, there were a small number, a handful, of subjects who did enter the clinical trials with cancer or on steroids and one cannot infer anything definitive, obviously, from just

a handful of subjects, but no safety concerns accrued.

The second, there were a number of individuals in the Shingles Prevention Study and in the other studies who developed immunocompromising conditions or required corticosteroids or other immunosuppressors shortly after vaccination, and no adverse experiences were noted there over and above what was seen in the general population.

Third, I would like to go back again to VARIVAX where the vaccine has been used in a very large experience over many years. Recall that although not indicated as such in the United States, the vaccine was initially developed for use in leukemic children and through studies that have been conducted by ACTG and others, the vaccine has demonstrated a very acceptable safety profile in immunocompromised populations.

And so in terms of that particular aspect of generalizability, what we are proposing for our initial package circular is consistent with what we have studied. In fact, we will, beginning in 2006 now that we have analyzed the full safety database for

immunocompetent individuals, be looking judiciously to expand the populations for whom the vaccine would be developed, but those are for future studies. That is not for now.

In terms of the other exclusions from the Shingles Prevention Study, those were in some cases due to the immunodeficiency exclusion criteria, but several of the other criteria were more practical considerations for that study only given the fact that people needed to have frequent contact with sites, needed to have long-term follow-up, needed to get back and forth.

And so the enrollment for that study was built around largely ambulatory subjects. There were two sites that did some recruitment and enrollment at nursing homes. We went back and tried to verify exactly how many and who these were, could not get exact numbers.

But separate from the ambulatory issue, per say, I want to go back to the functional status that was evaluated and, based on a functional status measure taken at baseline, there were, approximately,

half of the enrolled subjects who were mildly, moderately or severely limited at baseline, about 10 percent moderately or severely limited at baseline, and the profiles that were seen were largely the same across those groups.

DR. FLEMING: Let me ask for maybe more concise answers, because I have got several questions and I know time is limited. But the bottom line is it's unfortunate not to have more data on these particularly important high risk groups.

I am confused about the exclusion of the 50 year-olds. When you were giving slide S-13 and S-39 you were justifying their exclusion logically when the study was designed in part because, as your data do show, PHN risks are very low until you're age 60. But your closing slide, S-79, then says EpiData strongly established the clinical need above age 50. It seems inconsistent.

DR. SILBER: Yes. The question is about age 50 and the decision to not enroll or not target age 50 initially, but to target age 50 subsequently, is actually consistent with the scientific data

knowledge regarding --

DR. FLEMING: Well, basically, you only thought you were going to affect pain at the beginning and then you actually more affected zoster risk and, hence, now you believe that 50 years-olds are going to potentially benefit? Is that the concise answer?

DR. SILBER: Let's separate out the medical need on the one hand and then the ability of the vaccine to meet that need on the other hand.

Several population-based epidemiologic studies suggest that on the order of 200,000 episodes of herpes zoster occur each year in this country among people 50 to 59 years of age. The acute episode for people in their 50s is as severe, requires as much medical therapy, requires as many doctor visits and results in on average five work days lost. So based on the magnitude of that, the need is there.

DR. FLEMING: Could you put up S-13? I need a much more quick answer, S-13. As you were describing when you designed the trial and you were focusing on PHN and severity of zoster cases --

DR. SILBER: Correct.

DR. FLEMING: -- you noted that risk is small below age 50, below age 60. That is still, in fact, what you would view to be the truth, correct?

DR. SILBER: That is correct, that the risk of PHN begins to rise substantially at 60.

DR. FLEMING: Next question. Why only 2 percent blacks?

DR. SILBER: 2 percent blacks? Is that what --

DR. FLEMING: Right. Why are there only 2 percent in the study population, blacks?

DR. SILBER: Yes. The Shingles Prevention Study was open to the general population and was advertised in the general community, and this is something that we acknowledge and have been making efforts to increase enrollment of minority populations in studies. It was a bit of a surprise to us as well, I must admit, and the recently completed studies have included substantially more minority individuals.

DR. FLEMING: Two more very quick questions. One safety question and to make it short, I will just ask for some data we can be presented

later on. When we look at the Safety Substudy, there is a 60 percent relative increase in SAEs and it's an 80 percent relative increase in SAEs when you're above age 70.

Could we get a summary of what those SAEs are? And, secondly, could we get a summary of overall hospitalization by arm for the entire cohort of 38,000 and, specifically, zoster-related hospitalization by arm and serious morbidities by arm? If we could get those data, that would be helpful.

My last question up front here relates to the burden of illness score. My understanding is you're looking at, in essence, the average. You look at that burden of illness score and the duration of time that you have that score and the product then, in essence, gives you that total burden.

So if somebody had a score of 4 and somebody had a score of 3 and they were the same duration over 182 days, then that would be a ratio of 4:3. If somebody has a score of 3 and somebody else has a score of 2, it should be 3:2.

But if, in fact, someone has a score of 3

over the 182 days and someone has a score of 2 over the 182 days, does that come out as 3:2 or is the 3 counted for all 182 days and the 2 only counted for 30 days, in which case you're getting a radical misrepresentation of that 3:2 ratio?

DR. SILBER: The question relates to the use of the BOI and the BOI was designed to look specifically at pain scores of 3 or higher because of the validation that suggested that pain scores of 1 or 2 were not clinically meaningful in terms of daily activity. So, yes, scores below 3 --

DR. FLEMING: So is what I'm saying correct?

DR. SILBER: -- were not included in the scores, the overall scores for the vaccination or placebo groups.

DR. FLEMING: So you impute a score of zero after day 30 for people whose scores aren't above 3. Is that correct?

DR. SILBER: That is correct.

DR. FLEMING: And could you show us on S-52, you come up with a P of 008 for the contribution,