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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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148TH MEETING OF THE VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

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September 13, 2017
8:30 a.m.

FDA White Oak Campus
Building 31, Great Room (Salon B&C)
10903 New Hampshire Avenue
Silver Spring, MD 20993

KATHRYN EDWARDS, M.D.	Chair
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HANA EL SAHLY, M.D.	Voting Member
HOLLY JANES, Ph.D.	Voting Member
KAREN KOTLOFF, M.D.	Voting Member
RUTH LYNFIELD, M.D.	Voting Member
SARAH LONG, M.D.	Voting Member
MARK SAWYER, M.D.	Voting Member
MELINDA WHARTON, M.D., M.P.H.	Voting Member
KARIN BOK, M.S., Ph.D.	Temporary Voting Member
SHELDON V. TOUBMAN, J.D.	Consumer Representative
DAVID GREENBERG, M.D.	Industry Representative

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OPEN PUBLIC HEARING SPEAKER

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INDEX

INDEX

M E E T I N G

(8:34 a.m.)

DR. EDWARDS: Good morning. I would like to welcome you to the Vaccines and Related Biologics Products Advisory Committee today. Today the topic will be to discuss and make recommendations on the safety and the effectiveness of Zoster Vaccine Recombinant, Adjuvanted Shingrix, manufactured by GlaxoSmithKline Biologics.

I would like to begin by first welcoming everyone that is here, welcoming the Committee members, the Sponsor, the people in the audience, and also welcoming the viewing webcast. I know that many of you are out there multitasking as you listen to us this morning.

Before we begin, I would like to start going around this table so everyone will know each other on the Committee, and to just introduce yourself, to say where you're from and very briefly what you do.

Paula, would you like to start?

DR. AGGER: I'm Dr. Paula Agger. I'm the clinical reviewer on the file.

DR. GRUBER: My name is Marion Gruber. I'm the Director of the Office of Vaccines.

DR. BOK: Good morning. My name is Karin Bok. I am a vaccines science and vaccine safety advisor to the director of the National Vaccine Program Office.

DR. EDWARDS: Dr. Kotloff is stuck in traffic but will be here momentarily. She's from the University of Maryland and a very well-known vaccinologist.

Ruth.

DR. LYNFIELD: Ruth Lynfield. I'm the state epidemiologist and Medical Director at the Minnesota Department of Health.

DR. LONG: I'm Sarah Long. I'm a pediatric infectious disease doctor, Chief of Infectious Diseases at St. Christopher's Hospital for Children in Philadelphia, and an associate editor of the Red Book Report of the Committee on Infectious Diseases of the American Academy of Pediatrics.

DR. JANES: I'm Holly Janes. I'm a biostatistician at the Fred Hutch, and I work in clinical trials of vaccines.

DR. ENGLUND: I'm Janet Englund, a Professor of Pediatric Infectious Diseases at the University of Washington and Seattle Children's Hospital.

DR. WHARTON: I'm Melinda Wharton, and I'm currently Acting Director of the National Vaccine Program Office.

DR. EL SAHLY: Hana El Sahly, Associate Professor of Infectious Diseases at Baylor College.

DR. SAWYER: I'm Mark Sawyer. I am a pediatric infectious disease physician at the University of California, San Diego, and I also work with my local health department on vaccine delivery.

MR. TOUBMAN: I am Sheldon Toubman with New Haven Legal Assistance Association. I am a consumer advocate, particularly in the area of Medicaid.

DR. GREENBERG: David Greenberg, pediatric infectious diseases, adjunct associate professor at the University of Pittsburgh and serving as the Industry Representative. I'm with Sanofi Pasteur.

DR. EDWARDS: Thank you very much.

I'd like to now ask Captain Serina Hunter-Thomas to make some administrative announcements and read the Conflict of Interest Statement.

CAPT HUNTER-THOMAS: Thank you, Dr. Edwards. Good morning, everyone. On behalf of the FDA and the Center for Biologics Evaluation and Research and VRBPAC, we would like to welcome you all today to the 148th VRBPAC meeting. Dr. Kathryn Edwards is the Chair for VRBPAC.

And today's session has one topic that is open to the public in its entirety. The meeting topic is described in the *Federal Register* notice that's been posted.

FDA/CBER has press media representatives here today. Mr. Paul Richards, who is standing in the back, hand raised, is here. And later on today Ms. Lyndsay Meyer will be here as well.

The transcriptionist for this meeting today is from Free State, and his name is Mr. Tom Bowman. When you make your

comments or ask any questions, please speak up so that he can record all of your statements.

I would like to remind everyone to please check your pagers and your cell phones, and please make sure that they are either turned off or in silent mode.

When speaking, please first state your name so that we can record it for the record, and talk into the microphone so that you can be heard clearly for the record.

I have also been asked to request staff to inform the Committee members that if you haven't done so already, please preorder your lunches, and Rosanna Harvey will take care of the logistics of that.

I would like to now proceed with reading the Conflict of Interest Statement.

The Food and Drug Administration is convening today, September 13th, 2017, for the 148th meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

At this meeting, in the open session, the Committee will discuss and make recommendations on the safety and effectiveness of Zoster Vaccine Recombinant, Adjuvanted, manufactured by GlaxoSmithKline Biologicals.

The following information on the status of this Advisory Committee's compliance with federal ethics and conflict of interest laws, including, but not limited to, 18 U.S. Code 208,

is being provided to participants at this meeting and to the public. This Conflict of Interest Statement will be available for public viewing at the registration table.

With the exception of the Industry Representative, all participants of the Committee are special government employees or regular federal government employees from other agencies and are subject to the federal conflict of interest laws and regulations.

Related to the discussions at this meeting, all members and consultants of this Committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouse or minor children and, for the purposes of 18 U.S. Code 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts and grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

FDA has determined that all members of this Advisory Committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S. Code 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential conflict of interest.

However, based on today's agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued under 18 U.S. Code 208.

Dr. David Greenberg is currently serving as the Industry Representative to this Committee. Dr. Greenberg is employed Sanofi Pasteur U.S. Industry representatives act on behalf of all related industry and bring general industry perspective to the Committee. Industry representatives are not special government employees and do not vote and do not participate in closed sessions.

Dr. Jeffrey Cohen is employed by the National Institutes of Health, at the National Institutes of Allergy and Infectious Diseases, Laboratory of Infectious Diseases. Dr. Cohen is a regular government employee and is the speaker for this meeting. Dr. Cohen has acknowledged his expertise in herpes viruses, including the varicella zoster which causes shingles. He clarified that he is not involved in any clinical trials involving either of these vaccines sponsored by GlaxoSmithKline or Merck.

Mr. Sheldon Toubman is serving as the Consumer Representative for this meeting. Consumer representatives are special government employees and therefore are screened for their financial conflicts of interest and cleared prior to their participation.

At this meeting there may be regulated industry speakers

and other outside organization speakers making presentations. These speakers may have financial interests 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.

The FDA encourages all other participants to advise the Committee of any financial relationships that they may have with any firms, its products, and if known, its direct competitors.

We would like to remind members, consultants, and participants that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to exclude themselves from such involvement, and their exclusion will be noted for the record.

This concludes my reading of the Conflict of Interest Statement for the public record, and at this time I would like to hand the meeting back over to Dr. Edwards.

Thank you.

DR. EDWARDS: Thank you very much.

I'd now like to begin the meeting with an introduction and a presentation of the questions that will be presented by Dr. Carmen Collazo-Custodio, who is a microbiologist at the

Division of Vaccines and Related Products at the FDA/CBER.

DR. COLLAZO-CUSTODIO: Thank you, Dr. Edwards, for your introduction.

Good morning, everyone. Today we're going to discuss Shingrix. This is an adjuvanted, recombinant herpes zoster vaccine manufactured by GlaxoSmithKline Biologicals.

In terms of today's agenda, after I provide a brief introduction on the topic, Dr. Cohen from the National Institutes of Health will discuss epidemiology and disease burden of herpes zoster in adults aged 50 years and older. GSK representatives will then make a presentation on the development of Shingrix. After lunch, we will convene to hear from Dr. Paula Agger, who will give the FDA presentation of the clinical data. This will be followed by the Open Public Hearing and the Committee discussion and vote.

Today I will provide a brief overview of a currently licensed herpes zoster vaccine in the United States, followed by a description of Shingrix and an overview of the biologics license application. To conclude, I will present the questions to the Committee.

Zostavax is the only currently licensed herpes zoster vaccine in the United States. Zostavax is a live attenuated varicella zoster virus vaccine manufactured by Merck. It is indicated for the prevention of herpes zoster (shingles) in individuals 50 years of age and older, and the vaccine is

administered as a single dose by subcutaneous injection in the upper arm.

Shingrix consists of a lyophilized recombinant varicella zoster virus glycoprotein E antigen that is reconstituted at the time of use with the AS01B adjuvant suspension. The antigen is a purified truncated form of the gE protein expressed in Chinese hamster ovary cells. And of note, the AS01B adjuvant is not contained in any currently licensed vaccine in the United States.

The AS01B adjuvant is composed of MPL from *Salmonella minnesota* and QS-21, which is a saponin molecule from the plant extract *Quillaja saponaria* Molina. MPL and QS-21 are combined in a liposomal formulation consisting of DOPC and cholesterol in phosphate-buffered saline solution. And you're going to hear more about this adjuvant during the presentation from the Applicant.

Shingrix is supplied as a vial of lyophilized recombinant gE antigen, which is reconstituted at the time of use with the accompanying vial of AS01B adjuvant suspension. After reconstitution, each 0.5 mL dose of the vaccine contains 50 µg of gE antigen, 50 µg of MPL, and 50 µg of QS-21. Shingrix is administered intramuscularly in two doses at Month 0 and Month 2.

The Applicant is proposing the following indication for Shingrix for the prevention of herpes zoster (shingles) in

adults aged 50 years and older. By preventing herpes zoster, Shingrix reduces the overall incidence of postherpetic neuralgia.

Now, the Applicant submitted a biologic license application for Shingrix on October 21st, 2016. The clinical package included data from two randomized, placebo-controlled, observer-blind clinical endpoint studies which evaluated vaccine efficacy. The studies are Zoster-006, which enrolled subjects 50 years of age and older, and Zoster-022, which enrolled subjects 70 years of age and older. The BLA also contained additional supportive clinical studies for a total vaccine exposure of greater than 17,000 recipients. And, again, you're going to hear the details of this clinical package from both the Applicant and the FDA presentations today.

Now, today the Committee, as you heard, is being convened to review and discuss presentations of safety and efficacy data derived from studies conducted with Shingrix. The Committee will be asked to vote on the following questions:

Are the available data adequate to support the efficacy of Shingrix for the prevention of herpes zoster (shingles) in adults 50 years of age and older?

Are the available data adequate to support the safety of Shingrix when administered to adults 50 years of age and older?

And this concludes my presentation. Thank you for your

attention.

DR. EDWARDS: Thank you.

Are there any questions?

(No response.)

DR. EDWARDS: Thank you.

We will now have Dr. Cohen from the NIH, the Chief of the Laboratory of Infectious Disease, discuss the epidemiology and disease burden of herpes zoster in adults age 50 years and older.

Jeff.

DR. COHEN: Good morning. So in terms of disclosures, I have no -- I'm not involved in any clinical trials of either the GSK or Merck vaccine. I do serve on two federal committees related to the matter coming before the Committee, and you can see those on the slide here.

So as we all know, primary infection with varicella zoster virus results in chicken pox or varicella. This is a disease that's associated with viremia, and you can see a diffuse rash on the skin, and the virus establishes latency and can reactivate later in life to cause zoster, or shingles, usually in a dermatomal pattern as shown on the upper slide.

The virus enters the dorsal root ganglia or the cranial nerve ganglia, where it establishes latency, and this can either be -- the dorsal root ganglia either can be infected by viremia from the blood or by ascending the axon from skin

lesions to establish latency in the dorsal root ganglia. And then later in life the virus can reactivate and come down the axon to cause the lesions associated with zoster.

So if one looks at individual neurons in healthy individuals who've had chicken pox years later in life, and we looked at over 1,700 in our laboratory, you can see that about 4% of the neurons are positive for varicella zoster virus, and the average copy number of VZV was about seven copies per neuron.

So in terms of epidemiology of zoster, the annual rate is about 3 to 4 cases per 1,000 persons per year. There are about a million cases of zoster each year in the United States, and the rate of zoster appears to be increasing. Unvaccinated persons who live to be up to 85 years old have a 50% risk of developing zoster in their lifetime, and about 3% of them will require hospitalization.

Now, as I mentioned, there's been increasing rates of zoster, and probably the best study that's looked over time from 1945 to 2010 showed this progressive increase in the rates of zoster per 1,000 person-years. And you can see that this rate of increase occurred even before the varicella vaccine was licensed and as well as before the zoster vaccine was licensed. This increase is seen in all age groups, not just in the elderly, and it's unlikely to be due to the varicella vaccine. And in the primary paper here, they did a statistical test and

found that there was no statistical relationship between the onset of the varicella vaccine and the increasing rates of zoster. It also seems to be increased regardless of the increased number of immunocompromised individuals or the use of antiviral therapy.

So risk factors for zoster, of course, are increased age, which is the major risk factor for zoster in healthy individuals, and these individuals have not seen chicken pox in quite some time, and presumably their T cell immunity has declined to varicella zoster virus.

Also, immunocompromised patients will have impaired T cell immunity. These include transplant patients, patients with hematopoietic diseases, like leukemia and lymphoma, or individuals with HIV.

And the common denominator here with age and immunocompromised is reduced varicella zoster virus-specific T cell immunity.

So, again, the virus is latent in dorsal root ganglia along the spine or in the cranial nerve ganglia underneath the brain, and the virus can reactivate to involve the skin and dermatomes or the skin of the face.

So if one has reactivation in thoracic ganglia, dorsal root ganglia T1 and T2, one gets a rash on here and in C5 and C6, one gets a rash shown here on the arm. So, again, just the dermatomal pattern associated with reactivation.

And one can have V1 distribution of the trigeminal ganglia. Again, this is a unilateral rash, doesn't cross the midline, and you can see that in this patient here.

So, again, the rash is usually in a dermatomal pattern, does not cross the midline, can involve two or three dermatomes in healthy individuals, and it's not uncommon to see a few lesions outside the dermatome probably associated with a low level of viremia seen in healthy individuals. The rash is more common in certain ganglia, such as thoracic and lumbar. New lesions occur over 5 to 7 days, and crusting takes up to about 12 days. And some patients, rare patients, don't have a rash but will have pain, referred to as zoster sine herpete.

The pain is often localized if there's increased sensation prior to the rash, often a tingling or numbness, and at that time it's difficult to make a diagnosis of zoster without the rash. The pain can be continuous or episodic, and it can present with abdominal pain or chest pain, making the diagnosis quite confusing. And up to 10% of individuals, particularly younger individuals, may not present with pain but just with a rash.

Now, zoster-associated pain is shown here, and the duration of pain after zoster, you can see, can persist many months after the onset of zoster. So if we look at 1 month after the onset of zoster, you can see about 50% of individuals will have pain and about 25% of them will have clinically

significant pain and about 5% severe pain. But, again, this pain can persist for many, many months after the onset of zoster. And in this particular study, the mean age of the individuals was about 66 years old.

Now, the most common complication of zoster is postherpetic neuralgia. It's thought that the second most common complication are skin infections such as *Strep* and *Staph* followed by ophthalmologic complications followed by neurologic complications. But postherpetic neuralgia, the most common complication, is probably the most dreaded complication of zoster as well. There are different definitions, but most of the studies will have a pain persisting for 90 days or more after the onset of the rash. And, again, the pain can persist for months or even years. It's associated with neuronal cell body and axonal degeneration with scarring of the ganglia. And, again, it's more common in individuals over age 50, and the older you get, the more likely you are to have postherpetic neuralgia as a complication of shingles.

Now, postherpetic neuralgia is a real problem for individuals. It's associated with chronic fatigue, weight loss, insomnia, physical inactivity, anxiety, difficulty concentrating, depression, suicidal ideation. These individuals often become withdrawn, don't socialize as much, and it really interferes with the activities of daily living and has a major impact on individuals.

And in terms of treatment of postherpetic neuralgia, I like this quote from Johnson and Rice's paper in the *New England Journal of Medicine*: In clinical trials of available therapies for postherpetic neuralgia, fewer than half of patients with postherpetic neuralgia had a 50% reduction in pain, and the adverse events associated with therapy for postherpetic neuralgia are common, particularly in the elderly patients among whom the disorder is most prevalent. So PHN is actually a difficult disease to treat, and oftentimes we're not very successful, and there are a lot of side effects associated with treatment in the elderly.

Each year there are 100,000 to 200,000 cases of postherpetic neuralgia each year in the United States. Ten percent of the zoster patients have pain lasting over 90 days. Eighteen percent will have pain lasting over 30 days. And it's most common in individuals who present with severe pain with zoster or individuals who have a large number of lesions associated with zoster.

And this slide from the CDC shows, again, that the rates of zoster increase as one gets older, and similarly, the rates of postherpetic neuralgia increase as one ages.

So in addition to postherpetic neuralgia, there are additional neurologic complications associated with zoster. These include Bell's palsy, a unilateral facial paralysis; Ramsay Hunt syndrome with vesicles inside the ear, numbness on

the anterior tongue, and again, facial paralysis. One can have hearing impairment, motor neuropathy, transverse myelitis, meningitis, Guillain-Barre syndrome, and one can also have stroke or TIAs. Here we see narrowing of carotid arteries associated with vasculitis during zoster, or it can occur months after zoster. So there can be a lot of morbidity associated with zoster.

In addition, ocular complications are not uncommon. The disease can involve, really, any part of the eye due to reactivation of the ophthalmic branch of the trigeminal ganglia, and 15% of zoster cases will involve the eye. It can result in keratitis where you can see inflammation of the cornea, uveitis in the middle of the eye, retinitis in the back of the eye, or glaucoma. And if the eye is involved, it's important to have an ophthalmologic consult because additional therapies are often needed.

As I mentioned, bacterial superinfections with *Strep* and *Staph* can be a complication. Individuals can have disseminated disease, postherpetic itching, and the disease can also be transmitted, or I should say varicella zoster virus can be transmitted to children, causing varicella, although zoster is about one-fifth as infectious as varicella. So we recommend contact precautions for individuals with dermatomal zoster and airborne precautions for individuals who have disseminated diseased or are immunocompromised.

In individuals with impaired cellular immunity, new lesion formation can continue for even longer, up to 2 weeks. Healing can take longer. And these individuals can have disseminated disease, not just dermatomal disease, as you can see on the back of this unfortunate individual. And the disease can involve the viscera, including pneumonitis, hepatitis, encephalitis, or vasculitis or vasculopathy.

And, again, in immunocompromised individuals, there is more of a high-level viremia resulting in dissemination of the virus to different organs, whereas in non-immunocompromised individuals, the virus usually reactivates again from the dorsal root or cranial nerve ganglia, resulting in this limited dermatomal rash. However, again, one can often have pain and additional complications.

If there's an AV person, I could use a little help with advancing to the next slide. Thank you.

So individuals who are impaired, with impaired cellular immunity, such as patients with HIV, can have additional complications: warty verrucous lesions as shown here, acute retinal necrosis, or progressive outer retinal necrosis. And they can develop acyclovir-resistant zoster, which can be more difficult to treat. Patients who have stem cell transplants can have reactivation from other ganglia, including the celiac ganglia, and present with pancreatitis or hepatitis. And the disease can be very severe in these individuals, and a rash may

only develop later, such that they may be treated later, and as a result, some of these individuals can die from the visceral disease because it often is treated late.

In terms of the immunology of zoster, many of these individuals, when they present, can have normal levels of antibody to VZV. But, again, the disease is due to impaired cellular immunity to zoster, to varicella zoster virus, particularly impaired CD4 cells.

And as we know, cellular immunity declines with age. Shown here is cellular immunity as measured by a skin test similar to PPD but using VZV glycoproteins, as done in Asia often, and/or cellular immunity measured by impaired lymphocyte stimulation indices, more often used in the United States. But as one gets older, the cellular immunity to VZV declines, and one is at a higher risk for developing zoster.

So in terms of economic burden of zoster, one of the best studies was done by Barbara Yawn, who I think is here today, and this was a study done, carried from 1996 to 2001 in Olmstead County, Minnesota, and you can see that of patients with zoster, the mean cost to treat per patient was about $1,300. This increases about three and a half to fourfold if one has postherpetic neuralgia, and it increases further if one has complications associated with zoster, including ocular complications, neurologic complications, dermatologic complications, or other complications such as disseminated

disease. So, again, about $1,300 per case of zoster.

Now, if one is treating immunocompromised patients, again, the increase -- there's a further increase in the average cost per patient of $3,600 per case. And this study involved about 1,700 individuals in Olmstead County. About one-tenth of them had PHN, and about a tenth of them had non-pain complications.

So the authors concluded, by extrapolating, that the cost to the United States per year was about $1.1 billion in medical costs. And if one looks at additional studies, the range of cost is about $1.1 to $1.9 billion per year for zoster, and this does not include an additional $1.6 billion in loss of productivity of these individuals. And these costs are based on 2006 dollars, not 2017 dollars.

So additional data from that paper shows the percent of cost due to hospitalization, and you can see that patients who have complications accounted for about 50% of the hospitalization costs; those with PHN, about 40% of hospitalization costs; and those without complications, about 15%. And, again, if one looks at the costs broken down by hospitalizations, emergency department visits or outpatient visits, again, most of the costs are associated with outpatient visits, particularly in those with postherpetic neuralgia or complications compared to those without postherpetic neuralgia. But there are also costs, of course, due to emergency room visits and just outpatient, no hospitalizations.

In general, hospitalizations are most frequent for medication for immunocompromised individuals or for dehydration or pain management in the elderly, sort of failure to thrive.

Also, in terms of costs associated with zoster, if you look at the mean cost per patient, those who underwent hospitalization, you can see it's close to $250; emergency room visits, it's close to $100; outpatient visits, $300; prescriptions, up to $400.

And if you look at the medication costs for all patients with zoster, antivirals followed by analgesics were the most common medication costs; for patients without PHN, it was antivirals; those with PHN, analgesics as well as antidepressants and antivirals.

And the cost of zoster increases with increasing age. Again, you can see the mean cost per patient: individuals 80 years of age or older, nearly $2,000 per patient, particularly associated with hospitalization and prescriptions. But this, again, increases as one gets older.

And also, if one looks at the, again, increasing age, again, costs are higher with those with postherpetic neuralgia, shown here in gray, than those with just zoster in general.

So another study was done with a much larger group of individuals. This is 39,000 patients with zoster and 1,700 with postherpetic neuralgia. This was based on the MarketScan Research database, data from 1998 to 2003, and you can see the

average cost per zoster patient, if you look at all ages, is about $1,100. And, again, in the prior study, it was about $1,300, so the numbers are quite similar here, despite the fact that these studies were done in difference in time and different methodology here.

Again, the cost for treating all postherpetic patients, again, this is per year, was about three and a half to four times the cost of treating patients with zoster. So, again, pretty much the same data in these two studies. And, again, as you can see, over time as individuals age, the cost of treating zoster often goes up. And, again, the authors of this study concluded, the direct cost of zoster may exceed a billion dollars in the United States, again, the same conclusion as from the prior study. So, again, the major cost is incurred by the elderly here.

And then, finally, from this study you can again see the immunocompromised individuals, shown by the black bars, again have a higher cost associated with treating zoster than those who are non-immunocompromised.

So in terms of how we treat zoster, antiviral therapy is recommended for those at highest risk of complications, and those are individuals greater than the age of 50, those with moderate or severe pain, facial or ocular involvement, or other complications. And we certainly treat our immunocompromised patients with antiviral therapy as well.

Treatment should begin within 3 days of the onset of the rash in non-immunocompromised patients or if new lesions are continuing to occur. And immunocompromised patients will often have prolonged virus replication, so we often treat those individuals even after the 72-hour window has closed.

In terms of antiviral therapies, acyclovir, famciclovir, and valacyclovir were all used to treat zoster, and they're all guanosine analogues. In general, we get higher levels, intracellular levels with famciclovir than acyclovir and higher serum levels with valacyclovir than acyclovir. So we often treat patients with either of these two drugs, usually for about 7 days if the individuals are not immunocompromised.

And studies have shown, by treating with these drugs, it reduces the time to new lesion formation, loss of vesicles, crusting, and reduced severity of acute pain for most of these drugs. And side effects are generally pretty mild.

Immunocompromised patients, if they need to be hospitalized, are treated with intravenous acyclovir. And if, rarely, immunocompromised patients have acyclovir-resistant virus, foscarnet is used.

Zoster-associated pain is more difficult to treat, and you can see a large variety of drugs that are sometimes used to treat these individuals, including opioids, sometimes steroids, gabapentin, pregabalin, tricyclic antidepressants, and lidocaine. And some of these drugs shown underlined here have

been shown to reduce the pain associated with postherpetic neuralgia.

Postherpetic neuralgia -- this is from another review article. Recommended treatments include topical therapies such as lidocaine patches or capsaicin, which is often not well tolerated; pregabalin, tricyclic antidepressants, opioids, which should be used with great caution because these individuals often have prolonged pain, and it's recommended that a pain specialist should be involved if one is going to be using opioids here.

And in terms of why and how we think the varicella vaccine -- excuse me, the zoster vaccine may work, so when one gets varicella, one gets an immune response to the varicella zoster virus, both antibody responses as well as T cell responses. These responses increase, and then over time they decline.

If one's exposed to the chicken pox virus, there's probably a boosting of the T cell immunity. Again, over time, the response may decline, and eventually one gets below the threshold needed to prevent zoster. So when one's T cell immunity declines enough over time, one's at risk for zoster, and eventually, zoster can occur. If one gets boosted with the zoster vaccine, this will boost the VZV T cell response and keep the patient out of the range here when zoster can occur. So, again, the idea of the vaccine is to boost the T cell

response to reduce the rate of or incidence of zoster here.

So there are two vaccines that have been used for varicella zoster virus, the varicella vaccine licensed in 1995 and the shingles vaccine, the live attenuated shingles vaccine licensed in 2006. Again, these were both developed by Dr. Takahashi in Japan from a live attenuated vaccine.

The zoster vaccine is the same virus as the shingles -- as the varicella vaccine, but it's given at a 14-fold higher titer. People with zoster already have antibodies to VZV. And both vaccines induce both antibody, which is thought to be the correlate of protection for preventing varicella, as well as cellular immunity, which is thought to be the correlation of protection against shingles.

So the large study that was done of the live attenuated vaccines, the Shingles Prevention Study, showed that the vaccine reduced the rate of both herpes zoster compared to placebo and the rate of postherpetic neuralgia compared to placebo over a 4.9-year period.

The vaccine efficacy does decline for zoster as one ages, so you can see the efficacy was about 64% in individuals age 60 to 69, but only 38% in individuals over age 70. Over age 80, the vaccine further declined in efficacy.

Now, the efficacy for postherpetic neuralgia apparently was unchanged with age, whether one was 60 to 69 or over 70 here.

So there have been other studies done after the Shingles Prevention Study with these same individuals. There's the Short-Term Persistence Substudy and the Long-Term Persistence Substudy.

Again, for the Shingles Prevention Study, these individuals were 4.9 years after vaccination with a mean follow-up of 3.1 years. The same individuals were followed an additional period of time for a mean follow-up between 3.3 and 7.8 years in the Long-Term Persistence Study here, with a mean follow-up of 3.7 years. The efficacy did decline over time: 51% to 40% to 21%.

Also, the studies were done looking at the efficacy of burden of illness, which is the association of pain over time, and again, that declined as well, as individuals were followed for a longer period of time. And the efficacy against postherpetic neuralgia also declined.

There's also been a study of the zoster vaccine in individuals 50 to 59, rather than the Shingles Prevention Study, which were individuals over age 60. Here you can see individuals were followed for up to 2 years after vaccination for a mean follow-up of 1.3 years, and the efficacy was about 60% in the ZEST trial.

So if one compares the Shingles Prevention Study with the Short-Term Persistence Study and the Long-term Persistence Study and follows these individuals over time and looks at the

efficacy for zoster over time, you can see that compared to placebo, the rates declined. For the Long-Term Persistence Study, it was no longer placebo arm, and historical controls from the Shingles Prevention Study and/or the Short-Term Persistence Study were used, which is why we see a range of efficacy here.

But you can see that after about 8 years, the efficacy here overlaps with the 0% efficacy here. So over time, you can see that the efficacy for zoster does decline, and this raises the question about booster doses needed for this live attenuated vaccine.

Similarly, the efficacy for postherpetic neuralgia declines over time, although we see confidence intervals that are much wider here.

And then for the burden of illness, again, over time the efficacy to prevent the burden of illness declines over time.

And the authors found that there was statistical significance for the vaccine -- for the burden of illness persisted to Year 10, but after that you can see the efficacy overlaps with 0%.

So those studies were -- those were studies that were done with -- in a controlled setting based on the Shingles Prevention Study.

This is a large study sort of in the real-world use of zoster from Kaiser Permanente Southern California, and you can

see that whereas the shingles study involved about 25,000 individuals, here you can see 176,000 individuals received the vaccine, and there were three times the number of unvaccinated individuals they used for comparison. And, again, you can see that the efficacy to prevent zoster declined over time, and you can see, after 6 or 7 years, the confidence intervals overlap with zero, so again emphasizing the presumed need for booster doses after some period of time.

So what I've mentioned is the efficacy for zoster, burden of illness, and postherpetic neuralgia, but even individuals who do get zoster despite getting the live attenuated vaccine, the median duration of pain in those individuals is less than those who got placebo, and the degree of pain is less in individuals who break through with the live attenuated zoster vaccine compared to those who get placebo.

So the vaccine is currently approved for individuals aged 60 and above or based by the ACIP, and it's licensed by FDA for individuals 50 and above.

There are contraindications to this vaccine for individuals who are immunocompromised, including those with hematologic malignancies; individuals who have CD4 counts less than 200 or less than 15% of their T cells or CD4 cells; individuals with major cellular immunodeficiency, such as transplant recipients or individuals with T cell deficiency; or individuals who are on high-dose immunosuppressive therapy

defined as greater than 20 mg of prednisone daily over a 2-week period or individuals who are TNF inhibitors; and, of course, individuals who are allergic to the components in the zoster vaccine.

So the rates of vaccination against zoster have gradually increased over time, but we still have rates that are relatively low for individuals, for vaccinating the individuals who need the zoster vaccine. And some of these reasons include a low initial uptake. There were initially problems with supply with this live attenuated zoster vaccine. The difficulty, in some cases, of individuals having to go to a pharmacy to procure the vaccine and take it to their physician for vaccination and generally don't do as good a job in vaccinating older individuals as we do vaccinating children.

And there's a perceived notion that zoster is perhaps not as serious as, for instance, *Strep pneumoniae,* and as a result, internists may not push the zoster vaccine as much as they push other vaccines.

So there's relatively more mortality associated with zoster; it may not be as high, but there's a huge morbidity, as I've tried to explain today.

So, in summary, without the vaccine, 50% of persons aged 85 will get zoster. The rate of zoster is increasing.

Postherpetic neuralgia, the most common and dreaded complication of zoster, is ultimately defined as greater or

equal to 90 days of persistent pain after the rash resolves.

The frequency of zoster and PHN increase with age.

In clinical therapeutic trials, fewer than 50% of individuals with postherpetic neuralgia have a greater than 50% reduction in pain, so there's a lot of morbidity, and we don't do a good job of treating postherpetic neuralgia.

And the cost of zoster in the United States, again, it's estimated to be $1 to $1.9 billion per year for medical costs alone, and an additional $1.6 billion for lost productivity.

And the current live attenuated zoster vaccine does reduce the rate of zoster and PHN, but as I mentioned, there are concerns about the duration of the effect of the vaccine, the need for booster doses over time, and the effectiveness of the vaccine in elderly as well as its limited use in highly immunocompromised patients.

So I'm going to stop there and see if there are any questions.

DR. EDWARDS: Thank you, Dr. Cohen, for that excellent presentation.

Are there questions? Dr. Long.

DR. LONG: In elderly adults who do not have recognizable immune-compromising conditions, is dissemination with zoster more common than in younger adults, 50, 60, who get zoster? Is there an increasing risk of dissemination with age?

DR. COHEN: I'm not completely certain about that, but

certainly the more -- the lower your T cell immunity to VZV, the more likely you are to have major complications like dissemination. So, in theory, an older individual will have -- the older the individual, the more impaired the T cell response will be, but I'm not aware of specific studies.

DR. LONG: So I'm thinking that it's not more common generally.

DR. COHEN: Um-hum.

DR. LONG: I'm a pediatrician, so I don't know this truly, but if that's the case and they're getting zoster because their cell-mediated immunity is impaired, I'm just trying to understand, as we look at the antibody data that we're going to see, if it is some part neutralizing antibody that protects against dissemination in some of the vast majority of people who have zoster or not.

And I'm also wondering a little bit, with decreased likelihood of silent re-exposures because of decreasing in varicella, if we're going to see 50-year-old people in the next 10 years who are going to start at a different point, asking different things of the vaccine. And do you have anything to say about any of that?

DR. COHEN: Yeah. So we think that the T cell response is a mechanistic correlation in terms of reducing the rate of zoster, and it's been shown that the antibody response does correlate with zoster but is probably not a mechanistic

correlate, meaning that it's associated with the -- the antibody is associated with a decreasing rate of zoster, but it is not probably responsible for that. Again, it's a correlate but not a mechanistic correlate.

As I mentioned, in the studies that have been done thus far, it has not been shown specifically that individuals with the onset of varicella vaccination, that there's been increased rates of zoster. And, again, there were statistical tests done looking at that, and they did not see a correlation there. But, you know, it's possible that with increasing time and increasing numbers, perhaps a correlation could be found. But at the present time, I don't think there's any evidence that the varicella vaccine is resulting in the reason for the increased cases of zoster.

DR. EDWARDS: Dr. Greenberg.

DR. GREENBERG: Thank you for the presentation. I wanted to ask you about the increasing rates of zoster over the decades. You mentioned quite a number of reasons or thoughts that it's not caused from, including the fact that it -- I think, from what you said, it's increased in all the different age groups, you know, the older individuals.

So it leaves me with the question, is there any thought as to why the rates are increasing in the population? Have the results from Minnesota been replicated elsewhere? And are there implications from that increased rate that we should be

thinking of in terms of, you know, any vaccine that we want to administer in this population?

DR. COHEN: So the results of the -- so the Minnesota study is the one that I quoted just because it is the longest period of time, but there have been multiple other studies, also, which have shown that there are increasing rates of zoster, so it's not just a single study. It's really unknown why there are increasing rates. Some people say that perhaps zoster is better recognized and there may be more subtle presentations of zoster that are recognized than perhaps earlier on. But to be honest, I really -- we really don't know why the rates of zoster are increasing.

DR. LONG: Jeff, it does seem, at least from the data from the children who are being vaccinated, that overall, the rates of zoster in vaccinated children appear to be less than those that have natural diseases; is that correct?

DR. COHEN: That actually is correct. So in the very young -- again, I was charged to talk about zoster in 50 years and older, and you're absolutely correct that the rates of zoster in, like, 10-year-olds are lower than they are -- yes, with the varicella vaccine.

DR. LONG: It's hard for us pediatricians not to talk about kids sometimes.

DR. COHEN: Thank you for keeping me honest.

DR. LONG: Thank you.

DR. EDWARDS: Other questions?

(No response.)

DR. EDWARDS: Thank you very much, Jeff.

Do we want to take a break, or do we want to just keep moving on? Moving on?

UNIDENTIFIED SPEAKER: Move on.

DR. EDWARDS: Moving on, okay. All right, we will now begin the Sponsor presentations from GlaxoSmithKline, and they will be introduced by Dr. Kimber Poffenberger, Vice President and head of the North American Regulatory Affairs for GSK.

Good morning. Go ahead. Thank you.

DR. POFFENBERGER: Thank you.

Good morning, members of the Committee, FDA, and ladies and gentlemen in the audience. It is a real pleasure to be here today. I am, as was already introduced, Dr. Kimber Poffenberger, and I'm head of the North American Regulatory Affairs team for GSK Vaccines. GSK is pleased to be here today to discuss our candidate subunit herpes zoster vaccine with the proposed trade name Shingrix.

Our presentation today will follow this agenda. After I provide a brief introduction, Dr. Barbara Yawn, Adjunct Professor, Department of Family and Community Health at the University of Minnesota School of Medicine, will describe the disease epidemiology of herpes zoster in the U.S.

Dr. Arnaud Didierlaurent, head of the GSK Adjuvant

Platform, will then describe how GSK developed Shingrix, which is composed of a recombinant VZV glycoprotein E antigen and an adjuvant system AS01B.

Dr. Jacqueline Miller, head of clinical research for the GSK Vaccines U.S. R&D center, will then describe the clinical development program and review results obtained from the key studies. She will review the efficacy and immunogenicity of Shingrix in preventing herpes zoster across all age groups 50 years of age and over.

Dr. Jens-Ulrich Stegmann, head of Clinical Safety and Pharmacovigilance, will then review the safety profile and the pharmacovigilance plan.

And, finally, Dr. Miller will review the benefit-risk of Shingrix and conclude our presentation.

We're here today for three key reasons. First, as you heard previously, there is a medical need. Shingles, or herpes zoster, is a common painful disease caused by the reactivation of the chicken pox virus, varicella zoster, which will impact about one-third of us in our lifetime. This risk increases as we age or with immunocompromising conditions. Herpes zoster can lead to serious complications, including postherpetic neuralgia.

Second, we're here to share how GSK specifically developed this vaccine to address the challenge of immune decline that underlies the medical need. We will refer to Shingrix vaccine

in our presentation as HZ/su.

Finally, we are here to discuss our clinical program and to share the robust data from two Phase III studies which demonstrate that HZ/su has high vaccine efficacy against herpes zoster and its complications, with efficacy maintained for at least 4 years after vaccination in all age groups studied.

Our vaccine combines a recombinant subunit antigen with an adjuvant. The selection of the antigen and adjuvant combination was based on development studies and extensive clinical data. The subunit antigen was selected because it is a non-live antigen from a conserved portion of the surface of a VZV-infected cell, gE. And as a recombinant protein, it can be lyophilized and stable. The adjuvant system, AS01B, was selected to ensure a strong and persistent immune response.

After two doses, this antigen and adjuvant combination induced a strong and sustained gE-specific humoral and cell-mediated immune response regardless of age.

The proposed indication of our initial application is for the prevention of herpes zoster in adults 50 years of age and older. By preventing herpes zoster, Shingrix reduces the overall incidence of postherpetic neuralgia. A two-dose schedule is proposed with a second dose administered between 2 and 6 months after the first dose.

Before we move on to the rest of the presentation, I would like to provide you with a brief overview of the U.S.

regulatory timeline. We followed a classic development process for HZ/su to fulfill regulatory requirements, interacting frequently with the FDA, including interactions to agree on the clinical development plan and the chemistry manufacturing and control plans. The BLA was submitted in 2016, and this brings us to our Advisory Committee meeting today.

GSK conducted an extensive global clinical development program with an overall clinical database of more than 32,000 subjects with more than 17,000 HZ/su recipients. Our early development program established the adjuvant and the antigen dose. We then conducted two large-scale Phase III efficacy and safety studies in subjects greater than or equal to 50 and greater than or equal to 70 years of age. We also conducted several standard, late development Phase III studies to support the label.

This global clinical development program for HZ/su delivered a large safety database with placebo control. Our two Phase III efficacy studies demonstrated overall efficacy above 90% in all age groups 50 and above. That efficacy has been maintained at high levels, remaining above 87% 4 years out.

I would now like to turn our presentation over to Dr. Yawn, who will describe the disease epidemiology of herpes zoster and its complications.

DR. YAWN: Thank you. And good morning to all of you. I

am Dr. Barbara Yawn and a paid consultant for the Sponsor. I have no financial interests or potential benefit from the outcome of these proceedings.

This morning I'm going to highlight some of the excellent review that Dr. Cohen has already done on the epidemiology and clinical burden of herpes zoster. This condition is unique among vaccine-preventable diseases. It's primarily a disease of adults, and it's caused by reactivation of the latent VZV virus rather than a primary infection. With zoster prevention, we're talking about preventing major morbidity in one in three U.S. adults.

This is a different schematic. Is there a way to get rid of that? Can I do something to get rid of it? I'll proceed, and when we get rid of it, you'll get to see the middle part, I hope. All right. Okay, thank you.

This is a schematic, a little different one, of the progression to herpes zoster. It begins with chicken pox, which prior to varicella vaccination usually occurs before adolescence and covered or could cover the entire body, characterized by airborne spread and the typical itchy widespread vesicular rash.

Chicken pox usually heals in 7 to 14 days, sometimes leaving the typical chicken pox scars, but the resolution is not complete. The body does not clear all of the VZV virions. They become latent in sensory nerve cell bodies in the dorsal

root ganglia and cranial nerves, probably, as was said, by retrograde axonal transport from skin sites or due to T cell viremia.

A reactivation occurs decades later with increasing age and accompanying immunosenescence. The virions begin replicating and spread down sensory nerve cells into the skin, usually within a single dermatome, resulting in the acute pain and dermatome vesicular rash of shingles.

This, which you've also seen, illustrates the highlights of the most important risk factors for zoster: age and accompanying immunosenescence. The primary varicella infection, or chicken pox, leads to the induction of the VZV-specific memory T cells, which is the rapid elevation of the blue line to a level that's associated with immunity. This immunity may be boosted periodically by silent reactivation from the latent VZV or, in the past, exposure to children with chicken pox. Those are the small peaks you see.

But with increasing age, VZV-specific immunity, especially cellular immunity, declines. At some point, usually after age 45 to 50, the VZV-specific immunity falls below the hypothesized immunological threshold -- that's the dashed line -- and zoster may occur. Zoster vaccine and vaccination is designed to push immunity back above this threshold.

Of the estimated one-plus million zoster cases in the United States each year, more than 65% are in adults age 50 and

older. In this slide you see the incident rate of zoster in each decade of adulthood, as well as the rates of postherpetic neuralgia, in orange, and you can see they go from less than 10% up to almost a quarter or a third of those in the oldest age group that have postherpetic neuralgia. You'll notice that the increase incidence begins before 50, not just in the oldest old, and it continues increasing throughout life. As the population ages, the annual 650,000 cases in adults 50 years and older are likely to increase, adding to the burden of zoster pain and complications.

Most cases of shingles are in immunocompetent individuals, illustrated here by the green bars in the histogram. For immunocompromised individuals, highlighted in orange, the severity of shingles acute pain and rash are usually greater, as are the rate and severity of complications. The cases in immunocompromised individuals currently are about 10 to 14% of all cases, about 100,000 to 140,000 of the 1 million annual cases in the U.S. However, with increasing use of immunocompromising therapies, this may increase.

Zoster has three important clinical phases, as mentioned. The prodromal phase begins with the onset of neuropathic pain, sharp, stabbing, burning, or intense itching that is frightening and severe enough to patients to bring about one in eight shingle sufferers to the emergency room or an office before the rash is apparent. Because there are no easily

distinguishing features at this time for the pain, it's seldom diagnosed as zoster and often results in many tests and imaging studies in an effort to diagnose the cause.

The acute rash phase begins with the appearance of the typical dermatome vesicular rash. While diagnostic, the rash is really not the main cause for morbidity in shingles, as you've heard. It's the severe pain, continuing for those with prodromal pain or beginning with the appearance of the rash. The pain is again described as stabbing, burning, or very intense itching, sometimes accompanied by allodynia or heightened skin sensation. This can be so intense that it's impossible for the sufferer to stand to even put clothes on over the rash.

Patients often describe this acute pain as at least a 4 to 7 out of 10, pain comparable to kidney stones or even the late stages of labor but without the waxing and waning of labor pains. The pain usually lasts until the rash heals or beyond for several weeks. At 90 days we label this pain as PHN, or postherpetic neuralgia, which then may continue for many more months. Eighty percent of PHN does resolve within 12 months. But for one in five people with PHN, especially the oldest, this will continue with daily pain for more than a year, greatly impacting their quality of life, ability to engage in self-care, markedly limiting family, social, hobby, or work activities. Try to imagine the impact of pain that keeps you

from doing what you want and need to do every day for weeks, months, or years.

But PHN is not the only complication, as you see from this slide. Zoster has several significant non-pain complications. Here you can see the rates of these non-pain complications and how they increase with age, as they do with severity. Most of these complications add further interference with usual activities and adversely affect the patient's quality of life.

The eye complications are some of the most worrisome for the patient and the physician. Concerns about iritis or corneal scarring resulting in vision loss and even spread to the CNS make this an automatic ophthalmology referral for nearly every case of herpes zoster ophthalmicus.

The impact of these complications was brought home to me when I developed Ramsay Hunt syndrome as a complication of my zoster, 2 weeks of facial rash and significant pain that kept me from seeing patients, and then another 6 weeks of a Bell's-like palsy, with my patients worrying that I'd had a stroke, a huge impact on my quality of life.

But of the symptoms and complications of zoster, it's the pain that is most common and most likely to adversely affect a patient and their family's quality of life.

PHN, as I said, can keep a patient housebound, missing work, hobbies, and even family celebrations. Imagine being unable to hold or play with your grandchildren for weeks,

months, or years. Even those who do not develop PHN can have acute pain that adversely affects daily activities for an extended period.

This graph is an example of one patient's trajectory of the daily worse pain and acute zoster. Note that the pain is measured on the Zoster Brief Pain Index, ZBPI, and doesn't fall below the threshold of 3 for over 2 months. That threshold is then associated with interference in a person's quality of life and ability to do their daily activities.

So let me summarize the challenges of treating the burdens of zoster. The prodromal pain, it's common and it's severe enough that one in eight will visit an emergency department or a doctor's office. Once the rash appears, diagnosis is reasonably straightforward, but the pain continues. We can prescribe antiviral medications, but even when prescribed within 72 hours of rash onset, they have a modest impact on reducing pain severity and promoting healing of the rash a day or so sooner. They do nothing to prevent PHN.

Complications require continuing and often specialized care. Once PHN is present, the choices for chronic pain management, as Dr. Cohen said, are not optimal. There's no cure, and therapy only reduces the pain severity, often with significant side effects such as drowsiness or unsteadiness with increasing risk of fall in these older patients. Opioids come with major risks and may not even help, according to a

recent Cochrane collaborative review.

Shingles is associated with major morbidity, and treatment is inadequate at all stages. Prevention seems to be a much better option. And prevention is now possible with a currently approved zoster vaccine. Approval of Zostavax was a very important addition to my clinical practice about shingles. However, the efficacy of that vaccine is limited, beginning at about 70% when vaccinating 50- to 59-year-olds and falling to 18% when vaccinating those 80 and older, as shown in this table from the Zostavax PI.

Not only is the efficacy not optimal, the effectiveness of vaccine wanes over time. You saw some of the slides from Dr. Cohen. This is, again, the longitudinal study from Kaiser Northern California that highlights the concern of the waning of activity down to almost no protection by 7 to 8 years post-vaccination. Other studies report slightly lower rates of waning, but all agree, effectiveness significantly decreases within 5 to 8 years.

So, with zoster, we're left with several opportunities for improvement. We have a common condition, more than a million cases a year. Almost all adults over the age of 40, more than 99%, are seropositive for VZV and therefore at risk of shingles; one of three of them will get shingles.

The population is aging, and the use of immunocompromising drugs is increasing, further increasing the pool of those at

greatest risk of zoster, its pain, and complications.

The primary burden of zoster is the associated pain experienced in prodromal, during the acute phase, and in 1 to 4 months for those that have PHN.

Treatment is not adequate for the acute or chronic pain of zoster, nor for most of the non-pain complications like herpes zoster ophthalmicus.

Prevention seems to be the answer, but currently available prevention has limited efficacy and marked reduction of protection over time, and it's not available for those that are immunocompromised.

Therefore, we're left with significant unmet needs in addressing the burden of herpes zoster, or shingles, in U.S. adults.

I'd now like to turn it over to Dr. Didierlaurent.

DR. EDWARDS: Could we have a couple questions, perhaps, before?

Okay, Karin. Dr. Bok.

DR. BOK: Thank you. Going back to the wonderful graph that you and Dr. Cohen presented about the immunity, cell immunity over time --

DR. YAWN: Yes.

DR. BOK: -- I'm just trying to understand. I know it's been over 20 years since the CDC recommendation for varicella vaccine. Have you been able to study how the immunity changes

over time for vaccinated kids compared to those exposed to the wild-type virus? I'm just trying to understand if in the future we might be reaching that threshold, younger than people that have been exposed to the wild-type virus.

DR. YAWN: The question about the levels of immunity --

DR. BOK: Yeah, yeah.

DR. YAWN: -- are beyond my competency to answer, and I believe some of my colleagues will be able to address that later. I think that you are highlighting something that is a hypothesized risk of will there be a shift in the age of shingles --

DR. BOK: Yeah.

DR. YAWN: -- as we move forward?

DR. BOK: Yeah, especially considering that, like Kathy mentioned, there's the herpes zoster in those vaccinated and maybe fewer silent reactivations as well. Yeah.

DR. BOK: Those are certainly considerations, yes.

DR. EDWARDS: Go ahead with the next speaker, then. Thank you.

DR. DIDIERLAURENT: Thank you and good morning. My name is Arnaud Didierlaurent. I'm the head of the Adjuvant Platform at GSK, and it's my pleasure to introduce the scientific rationale for the HZ/su vaccine.

Our vision was to develop a vaccine preventing shingles in populations with the highest unmet needs: first in older adults

to improve on standard of prevention, as discussed by Dr. Yawn; and second, immunocompromised individuals who are also at risk, at greater risk of developing zoster.

Now, whereas our proposed indication for the vaccine is today for individuals of 50 years and above, the vaccine was also designed to be equally effective in the immunocompromised, for whom there is no vaccines available.

Dr. Cohen and Dr. Yawn discussed earlier that shingles appear because the natural immunity to the virus, and in particular cellular immunity, is reduced and become inefficient in controlling the virus. An effective vaccine should restore this immunity to levels that can prevent reactivation.

While restoring cellular immunity is likely to be a prerequisite for the vaccine to work, antibodies may also play an important role. Here I'm showing the way antibody, beyond the capacity to neutralize the virus, can also support cell-mediated elimination of VZV-infected cells. Cell-mediated immunity, or CMI, mainly involves T cells. T cells could kill VZV-infected cells in two ways, either directly through effective cytokines or indirectly via natural killer cells, or NK cells, and killing infected cells, NK cells require the presence of VZV-specific antibody that decorate infected cells.

These mechanisms imply that both CMI and antibody are required to prevent VZV reactivation. Therefore, for a vaccine to be efficient, targeting both arms of the immune system is

considered to be important.

So in order to address the different challenges, we chose to develop an adjuvanted subunit vaccine. Because it is a subunit vaccine that does not replicate, it can be suitable for use in the immunocompromised.

Because older adults and the immunocompromised are classically less responsive to vaccination, the use of an adjuvant to enhance the response adds the potential to overcome the limitation of a declining or compromised immune system. And, in fact, it is now well established that adjuvanted vaccine can enhance immune response in older adults.

In contrast to a whole virus, highly purified antigen are usually poorly immunogenic. They lack the ability to stimulate the immune system. Adding an adjuvant to an antigen is expected to improve its immunogenicity, as shown here. This also results in improved persistence.

In addition, it has been shown that adjuvants increase the breadth of the antibody repertoire, not only modulating the level of the response but also the quality.

Several adjuvants are currently used in licensed vaccines, including three in the U.S., and one, namely an adjuvanted seasonal influenza vaccine, is approved for the older adult population.

In HZ/su, we selected gE as the recombinant antigen that provides specificity to VZV and the adjuvant AS01B; gE was

selected because it is expressed during reactivation and is a good target for the immune response. gE has a central role in the biology of the virus. It is essential for bio-replication but also for the virus to spread from cell to cell. Importantly, it is found at the surface of VZV-infected cells only when the virus reactivates. It is found on infected ganglia and skin lesions and is therefore highly visible to the immune system during reactivation.

gE is also a natural target for the immune system. The first exposure to VZV leads to a memory response to VZV antigens, including gE, and actually both gE-specific CMI and antibody are detectable in the vast majority of us.

In summary, the rationale for choosing gE combined with an adjuvant was to improve the capacity of the immune system to recognize infected cells and thereby prevent reactivation.

The adjuvant is called AS01B. "AS" stands for adjuvant systems because it is based on a combination of monophosphoryl lipid A, or MPL, immunostimulants used in the licensed HPV vaccine Cervarix, and QS-21, a saponin molecule. The liposome is used as a carrier for MPL and QS-21.

AS01 is part of a family of adjuvants developed by GSK and was designed more than 20 years ago by Dr. Nathalie Garcon and her team at GSK. It has been tested in various candidate vaccines in humans and has been shown to have an acceptable safety profile in more than 36,000 individuals in different age

groups and populations.

Among the different adjuvants, AS01 was chosen for its ability to generate the optimal profile of CMI and antibody for the zoster vaccine. Different adjuvants were compared in animal models, and AS01B compared to the other adjuvants, including alum, was superior in inducing T cell response. And this was very much in line with data in humans with other antigens.

Now I will summarize what we know about the mode of action of AS01. As other adjuvants, AS01B works by inducing a transient stimulation of the innate immune system at the injection site and in the draining lymph node. This is represented here on the left part of the diagram. This affects results in a transient inflammatory response characterized by cytokine induction and innate cell recruitment, such as those cells presenting antigens. This response lasts only for a few days but is critical to produce more gE-specific T cells and antibody that can later recognize VZV-infected cells, as shown on the right.

I will next briefly summarize the key principles on the mechanism of action of AS01. First, shortly after injection, AS01B components are recognized by specific -- sorry, by specific pathways of innate immunity, namely toll-like receptor 4 for MPL and caspase-1 for QS-21. The target cells of AS01B are macrophages in the draining lymph node.

Second, in a mouse model, when gE is not injected with AS01 at a different site, there is no increase in gE response. That told us that AS01 works only when co-localized with the antigen at the same injection site, and this occurs during a limited time window of 1 or 2 days.

And third, a unique synergy between MPL and QS-21 is the reason why AS01 is efficient at inducing cellular immunity. This is exemplified in a mouse model with preexisting immunity to VZV; gE-specific T cell response was much higher when MPL and QS-21 were combined in the liposome, as shown in the orange bar on the right, as compared to liposome alone, liposome with MPL, or liposome with QS-21.

This unique combination of MPL and QS-21 favors an efficient stimulation of gE-specific T cells and B cells, thanks to an increased number of activated antigen-presenting cells in the lymph node.

This early effect of AS01 eventually translates into an increase in gE-specific immunity, which is maintained for several years and can be mobilized in case of VZV reactivation.

Before testing the vaccines in humans, we performed a thorough preclinical evaluation of the potential toxicity of the vaccine, including the adjuvant components, according to regulatory guidelines. No safety concerns were identified.

So two early clinical studies were conducted to confirm the safety and immunogenicity profile of the vaccines in humans

and to validate its final composition. The first study, called Zoster-003 and the follow-up studies, 011, 012, and 013, are Phase II studies enrolling subjects with the age of 60 years and above and were designed to choose the antigen dose and number of vaccinations. The second study is Zoster-010, a Phase II study enrolling subjects of 50 years and above and designed to confirm adjuvant dose.

Before moving to the results of those studies, I'd like to go a little bit more into details about how we monitor the immune response to the vaccines in humans.

gE-specific T cells were measured by incubating blood cells overnight with a pool of peptide covering the entire gE sequence. The gE-specific cells are identified by flow cytometry based on their secretion of cytokines and the expression of the surface marker CD40 ligand. And the data are then expressed as the numbers of specific T cells expressing at least two of these markers.

For the antibody, we have used a classical ELISA assay to measure the amount of gE-specific antibody in blood. We've also used an ELISA-specific of the whole VZV as well as functional neutralization assay. These two assays confirm that, one, the antibody generated by the vaccines could recognize the whole virus, and second, that they were also functional.

For the rest of the presentation, we will only show gE

ELISA data as these are directly correlated with the other assays.

So here we see the number of gE-specific CD4 T cells over time. When comparing the group with gE alone, in gray, at the highest dose of 100 µg versus the same gE dose combined with AS01B, in green, we observed, as expected from a preclinical evaluation, a significant increase in the number of CD4 T cells when the adjuvant is used.

Now, on the right, you see a similar response in terms of anti-gE antibody concentration. This higher response persisted for 3 years, and this was regardless of age.

When comparing 100, 50, and 25 µg of gE, we found that overall the antigen dose had limited impact on the immunogenicity. But because the 25 µg dose was less immunogenetic than 50 µg, especially for antibody response, and because 100 µg did not provide significant improvement, we selected the 50 µg dose.

Finally, we investigated in this study the immune response after one or two doses. In blue are the data showing two dose schedules of 50 µg gE and AS01B, and this is the current formulation of HZ/su. The red line is one single dose of 100 µg gE in AS01B given after saline. Both antibody and cellular response were significantly higher after two doses as compared to one dose. This difference was maintained throughout the study period and, again, regardless of age.

And last, today I'd like to share with you Zoster-010 that was conducted to confirm the adjuvant dose. The results shown in the table are 1 month after the second dose.

In this study, we compared AS01B with its half formulation AS01E, as described at the top of the table. As shown in Zoster-03 study, adding AS01, whatever the dose, enhanced the CMI and antibody response when compared to gE alone, as you can see in the first column. When compared head to head, formulation of gE with AS01B significantly increased the number of gE-specific CD4 T cells by 30% and gE antibody response by 40%. This was seen across all age groups. So these results confirm the choice of AS01B as the adjuvant that induces the highest immune response VZV in order to maximize the vaccine capacity to prevent shingles long term.

To conclude, the results of these studies confirm that HZ/su induced the desired immune response profile, a high and durable cellular and antibody response against VZV in adults 50 years and above.

Second, these studies confirm the selection of the adjuvant AS01B, a key contributor of the long-lasting immunity induced by HZ/su.

And, finally, the 50 µg dose of gE combined with AS01B in a two-dose schedule was selected for further development.

I will now leave the floor to Dr. Miller, who is going to present the results of a Phase III efficacy study.

DR. EDWARDS: Please go ahead. We'll hold the questions until the end. Thank you.

DR. MILLER: Thank you, Dr. Didierlaurent.

Good morning. My name is Jacqueline Miller, and I am the head of clinical research and development at our U.S. vaccines R&D center. On behalf of GSK and the zoster team, it's my pleasure to present the clinical data for the HZ/su development program this morning. My presentation is in two sections outlining the efficacy and immunogenicity data.

I'd now like to give an overview of the clinical development program. It enrolled more than 32,000 individuals, including over 17,000 recipients of HZ/su in 19 clinical trials. Because of the time constraints, I'll not be able to review all of the studies with you, but I wanted to give you an idea of the breadth of work that's been completed. Studies which are discussed in the presentation are shaded, and those which are not discussed are unshaded.

Dr. Didierlaurent has already discussed some of the Phase I and Phase II studies.

EXPLO-CRD-004, Zoster-003, and Zoster-010 were conducted to select the final formulation and dose schedule of HZ/su. Zoster-003 was further extended to evaluate immunogenicity persistence post-vaccination. We will review the 6-year persistence time point, Zoster-024, later in the presentation.

The most important studies in our development program are

the large-scale Phase III efficacy and safety trials, and these will be the main focus of my presentation.

Zoster-006 or ZOE-50 was conducted in adults greater than or equal to 50 years of age, and it was paired with a nearly identical study, Zoster-022 or ZOE-70, in subjects over 70. In a preplanned analysis, key efficacy and safety endpoints from these studies were pooled to increase the statistical power.

As you will see throughout the presentation, we've added flags in the upper right-hand corner of the slides to orient you to which data are being discussed. Zoster-006 is represented in green, Zoster-022 in blue, and the pooled analysis from both studies in purple.

There were some additional Phase III studies which were conducted. These included Zoster-026, which demonstrated that a second dose of HZ/su can be given 2 to 6 months after the first; Zoster-004, a co-administration study with influenza vaccine; Zoster-007, a lot-to-lot consistency study; Zoster-033, where HZ/su was administered to patients who previously reported herpes zoster; and Zoster-032, which investigated subcutaneous administration.

So now we'll turn to the large-scale efficacy and safety studies, Zoster-006 and -022. Together, these two studies enrolled more than 29,000 individuals around the world. There were 18 countries included in North America, Latin America, Europe, Australia, and Asia, with 219 investigators

participating. This enrollment plan enabled experience with HZ/su in a broad population at risk for herpes zoster. In the United States, nearly 4,000 subjects were enrolled.

Zoster-006 and -022 were paired trials with similar designs. Investigators enrolled subjects in both studies in parallel. Subjects were randomized to receive HZ/su or placebo in a 1:1 ratio, and note that the HZ/su group is highlighted in orange and the placebo group in gray. This convention will be used throughout the presentation to highlight data from the two groups.

Both vaccines were given on a 0, 2-month schedule. The vaccination visits are highlighted by the turquoise icons on the slide.

In addition to vaccine visits, subjects returned to the study center for efficacy, immunogenicity, and safety follow-up. Active surveillance for cases of herpes zoster occurred at monthly visits or phone calls. Subjects were also queried about safety outcomes throughout the trial.

A subset of subjects were evaluated for immunogenicity. As Dr. Didierlaurent previously explained, we used the intracellular cytokine staining assay to measure cell-mediated immunity, and the ELISA assay to measure antibody concentrations to the gE antigen. An immunogenicity subset of Zoster-006 was assessed for CMI and humoral immunity, while a subset in Zoster-022 was assessed for humoral immunity alone.

Samples were obtained prior to vaccination, 1 month after the second dose, and then for persistence at 1, 2, and 3 years after the final vaccination.

We'll now review the study designs and objectives in more detail, and as there were many elements to these studies, we'll go through the design step by step.

The studies were stratified for age group to ensure broad representation. Zoster-006 was allocated 8:5:3:1 to four age strata: 50 to 59, 60 to 69, 70 to 79, and greater than or equal to 80 years of age.

Zoster-022 was specifically designed to enrich cases in the oldest age groups greater than or equal to 70 years of age or those at greatest risk for herpes zoster. Zoster-022 had an age stratification ratio of 3:1 for the 70 to 79 and greater than or equal to 80 years of age strata, which was exactly the same as for Zoster-006.

Both studies had a primary objective to demonstrate efficacy against herpes zoster in adults of the age cohort defined for that study. These were two of the four primary efficacy hypotheses for the studies.

The pooled analysis for the two studies also had two primary objectives: assessments of the efficacy of HZ/su against herpes zoster and postherpetic neuralgia in adults greater than or equal to 70 years of age. The pooled dataset in the older age group allowed us to enhance the number of

cases and enabled a more robust estimate of efficacy.

The other key objectives which I will review in this presentation include efficacy per age stratum, efficacy against PHN in adults greater than or equal to 50 years of age, reduction of herpes zoster complications other than PHN, and the immunogenicity of the vaccine. Evaluation of safety was an important objective in these studies and in all studies across our development program.

This slide presents the demography data of the total vaccinated cohort, or those subjects who received at least one dose of HZ/su or placebo in the overall study population, and those enrolled in the North American cohort, which included the U.S. and Canada.

The demographic characteristics were well balanced between the two groups in each study. More females than males were enrolled, and this is expected when conducting trials in an older population.

In terms of the racial distribution, the majority of subjects were Caucasian and Asian, reflecting the countries and regions where the studies were conducted. When we look at the North American cohort, more African Americans and fewer Asians and Hispanics were enrolled than in the overall population. Otherwise, the North American cohort was comparable to the rest of the regions.

Approximately 85% of those enrolled had at least one

comorbid condition. The treatment groups were comparable in terms of preexisting medical conditions such as hypertension, osteoarthritis, diabetes, and gastroesophageal reflux disease.

Before diving into the efficacy data, I would like to review how herpes zoster cases were captured in these studies. The case capture method was similar to that used for the licensed vaccine.

Subjects were trained, upon enrollment, to recognize a rash potentially indicating herpes zoster. If subjects experienced symptoms, they were instructed to visit the study center within 48 hours. The investigator would examine the rash and, if it was believed to be a suspected case, would obtain photos, clinical details, and three lesion samples for polymerase chain reaction, or PCR, testing.

Details of all cases were reviewed by a Herpes Zoster Ascertainment Committee, or HZAC, a group of five physicians with expertise in herpes zoster who were otherwise not associated with our study.

Two PCR assays were performed on each lesion sample, one for varicella zoster virus and one for a protein called beta-actin, which was used to ensure that the sample was adequate for DNA detection. PCR results were always considered the primary indicator of whether or not a case was herpes zoster.

If at least one of the three lesion samples was positive

for varicella zoster virus, it was a confirmed case of herpes zoster. And for cases which were confirmed as herpes zoster, approximately 90% of those were done through PCR.

If a sample was negative for varicella zoster virus but positive for beta-actin, the sample was considered adequate for DNA detection. Since no varicella zoster virus DNA was present, the case was confirmed as not a case of herpes zoster based on the PCR results.

However, if the sample was negative for both varicella zoster virus and beta-actin, then it was not considered adequate for DNA detection and the decision was referred to the HZAC. Although the HZAC reviewed all cases, this was the only scenario where the HZAC determined whether this represented a true case or not for the analysis.

A case decided by the HZAC had to be confirmed as yes or no by a unanimous vote. If one or more members were unable to decide, or the yes/no decisions were not unanimous, the case was not confirmed. The concordance between the HZAC assessment and PCR results, when they were available, was approximately 90%.

So now let's review the efficacy results. The table presents the number of cases and the overall incidence of herpes zoster in the HZ/su group on the left, the placebo group in the middle, and the calculated vaccine efficacy and associated 95% confidence intervals on the right. The overall

vaccine efficacy is presented, as is the calculated efficacy in each age stratum. This analysis was performed on the modified total vaccinated cohort, which included all subjects who received two doses of the appropriate vaccine and did not develop a confirmed case of herpes zoster within 30 days of the second vaccination.

Study 006 met its primary endpoint with vaccine efficacy of 97.2% for subjects greater than or equal to 50 years of age. The lower limit of the 95% confidence interval was 93.7%. The statistical criterion defining efficacy was a lower limit of 25%, so the primary hypothesis was met. The HZ/su group experienced a reduction in herpes zoster incidence from 9.1 to 0.3 per 1,000 person-years.

In each of the pre-specified age strata, 50 to 59, 60 to 69, and greater than or equal to 70 years of age, the observed vaccine efficacy was between 96.6 and 97.9%.

In addition, as shown in the sentence below, the observed -- an analysis was added to the statistical plan to align with the current ACIP recommendation to vaccinate adults over 60 years of age. The vaccine efficacy in this group was 97.6%.

HZ/su therefore achieved an unprecedented level of efficacy in a population of adults over 50 years of age, and this protection did not decrease with increasing age. This suggests that HZ/su can address one of the key unmet medical

needs for herpes zoster.

So now I'd like to review the efficacy results in adults greater than or equal to 70 years of age. The results I'm showing on the slide are for the pooled analysis, but the results are consistent with those of Zoster-022 alone.

The efficacy of HZ/su against herpes zoster in adults greater than or equal to 70 years of age was 91.3%, confirming the high efficacy observed in this population of Zoster-006. The primary efficacy hypothesis was also met as the lower limit of the 95% confidence interval was 86.8%, well above the statistical limit of 10%.

We again see similar efficacy estimates across age strata; in this case, even those over 80 years of age, which again addresses a key unmet medical need for the prevention of herpes zoster.

Because of the large sample size in these studies, we had the opportunity to estimate efficacy in a sensitivity analysis of each year of the efficacy follow-up. Over 25,000 subjects who were enrolled continued efficacy follow-up through Year 4. The efficacy was maintained at a level of at least 84% out to Year 4, in each year, in both age strata, indicating that the vaccine efficacy is durable. We're continuing to follow these subjects, and we will have revised efficacy estimates at 6, 8, and 10 years post-vaccination in an extension of the two Phase III studies.

So now I'd like to talk about the most important complication of herpes zoster, postherpetic neuralgia or PHN. We assess PHN by using the Zoster Brief Pain Inventory, or ZBPI. The ZBPI is a refinement of the Brief Pain Inventory assessment tool, which is a validated tool designed specifically to capture symptoms related to herpes zoster and was also used to assess the efficacy of a licensed vaccine against PHN.

Subjects with symptoms of herpes zoster were asked to complete the ZBPI for 28 days after symptoms started and then weekly thereafter until symptoms had abated for 28 days. A case of PHN was defined as a score greater than or equal to 3 for the worst pain experienced in a 24-hour period. This pain had to persist or occur 90 days after the first onset of symptoms.

This slide reviews the efficacy against PHN in subjects greater than or equal to 70 years of age, which was a primary endpoint, and greater than or equal to 50 years of age, which was a secondary endpoint. For the subjects over 70, the efficacy was 88.8% with a lower limit of the 95% confidence interval of 68.7%. The statistical criterion was met as this lower limit was well above zero.

The efficacy against PHN in those over 50 years of age was 91.2%, and the same statistical criterion was met with a lower limit of the 95% confidence interval well above zero. Note

that there were no cases of PHN reported in subjects 50 to 69 years of age who were vaccinated with HZ/su, and therefore, by preventing herpes zoster reactivation, HZ/su prevented PHN.

Herpes zoster can also result in important medical conditions other than PHN, although as both Dr. Cohen and Dr. Yawn mentioned, these occur much less frequently.

There were six additional complications of herpes zoster specifically captured in this study: ophthalmicus, disseminated disease, visceral disease, vascular disease, neurologic disease, and stroke. When we compiled all of these data together in a post hoc analysis, we found that the efficacy against herpes zoster-related complications other than PHN was 93.7% in those greater than 50 and 91.6% in those greater than 70 years of age, consistent with the other estimates of vaccine efficacy in these studies.

We also wanted to compare the worst pain experienced during a breakthrough case of herpes zoster in recipients of HZ/su to breakthrough cases in the placebo control group. This graph illustrates the aggregated worst pain scores reported by the HZ/su group, in orange, and the placebo group, in gray, over the first 28 days of an episode for which the ZBPI was completed.

The worst pain experienced in a 24-hour period is graphed on the y-axis as a function of time on the x-axis. The greater the area under the curve, the greater the disease burden of the

worst pain experienced by the study group. As can be seen by the lower area under the curve of the HZ/su group, lower worst pain scores were observed during herpes zoster episodes, suggesting that when the breakthrough disease did occur in the HZ/su group, the symptoms were lessened.

So, to conclude our review of efficacy, HZ/su was highly efficacious against herpes zoster and PHN. The efficacy against herpes zoster was 97.2% in adults greater than or equal to 50 and 91.3% in adults greater than or equal to 70 years of age. This efficacy was consistent through the age strata studied and persisted for at least 4 years.

The efficacy against PHN was 88.8% in adults over 70 years of age and 91.2% in those greater than or equal to 50. No cases of PHN were observed in subjects who were 50 to 69 years of age and received HZ/su.

Taken together, these data indicate that a single protein antigen combined with the AS01B adjuvant resulted in unprecedented efficacy in a population at least 50 years of age.

And unlike natural disease where the incidence of herpes zoster increases with age, the efficacy of HZ/su was consistent across the age strata.

For the breakthrough cases that did occur, there is evidence of reduced severity of the herpes zoster symptoms.

So now I'd like to discuss the immunogenicity of HZ/su.

The efficacy data we just discussed are the basis of licensure. The immunogenicity data are also important in terms of demonstrating the capability of HZ/su to induce both cellular and humoral immunity.

This slide reviews the immunogenicity data from Zoster-006 in terms of cell-mediated immunity in the left-hand graph and humoral immunity in the right-hand graph. This analysis was performed according to protocol for the immunogenicity cohort, which was defined as the group of subjects with no protocol violations who had immunogenicity data available. Let's first discuss cell-mediated immunity as reductions in CMI are known to predispose towards herpes zoster reactivation.

As you can see, 1 month after the second dose, the HZ/su group had a robust increase of 25-fold over baseline values, while the saline placebo group had essentially no change. As expected, there was a CMI drop in the HZ/su group over the first year, which reached a plateau and remained eightfold higher than baseline values 3 years after vaccination. And, therefore, CMI is restored with the induction of T cell memory after vaccination with HZ/su.

On the right-hand side of the slide we see the same pattern for the humoral responses. It's important to note that the y-axis begins at over 1,000 mIU/mL, and this is because most adults have been pre-exposed to the varicella zoster virus, and therefore there was a significant preexisting level

of antibody in both groups.

Once again, you see that there was a rapid increase in antibody concentrations in the HZ/su group to 42-fold over baseline values after the second dose, plateauing after the first year and maintained at ninefold above baseline values 3 years after vaccination.

One note: Because of the large sample size and logarithmic scales, the 95% confidence intervals are hard to visualize because of the tightness around the point estimate.

And, therefore, in addition to high vaccine efficacy, HZ/su induces both cellular and humoral immunity which is durable for at least 3 years.

Although persistence results are not yet available from the subsequent time points of the Phase III studies, we do have persistence data from one of the earlier clinical studies. The extension study, Zoster-024, involved continued follow-up of subjects from the antigen dose ranging study, Zoster-003, in which subjects were originally vaccinated when they were greater than or equal to 60 years of age. Dr. Didierlaurent already presented the immunogenicity data through Year 3 from this study. These subjects were followed for an additional 3 years to look at the persistence of CMI in humoral responses.

Note that because only the HZ/su group was followed for persistence, there's no control group to compare to in this instance.

Here we see a pattern that was very similar to the one I just showed you for the Phase III studies, a rapid increase in CMI and antibody concentrations after vaccination followed by a decline in the first year and then a plateau which is maintained in the subsequent years. Similar data are now available from the persistence time point 9 years after vaccination.

So, to conclude our discussion of immunogenicity, across studies we consistently see a rapid increase in CMI and antibody concentrations after vaccination, which persists above baseline out to 6 years post-vaccination. These persistence data complement the durability of efficacy observed in Zoster-006 and -022. And taken together, these data indicate that the combination of a single protein antigen with AS01B induces durable cellular and humoral immunity, addressing a key risk factor for the development of herpes zoster.

So now, moving to discussion of the safety data, I'd like to take this opportunity to introduce my colleague, Dr. Jens-Ulrich Stegmann.

DR. STEGMANN: Thank you, Dr. Miller.

Good morning. My name is Jens-Ulrich Stegmann, and I'm leading the Clinical Safety and Pharmacovigilance group in GSK Vaccines.

I will present to you a review of the safety data from the clinical program of HZ/su, and I will focus on data from

Zoster-006 and Zoster-022. But I will also give you a more in-depth insight about the analysis of serious adverse events and potentially immune-mediated diseases. I will conclude with a review of the proposed postmarketing pharmacovigilance plan for HZ/su.

Safety data for over 17,000 recipients of HZ/su were included in the submission to the FDA. In Zoster-006 and -022, more than 14,000 subjects received HZ/su, which represents over 85% of the safety database. This presentation will focus on the main safety pooling, a pre-specified analysis conducted on the pooled datasets of Zoster-006 and Zoster-022. This is because of the similar design of the two studies, as already outlined by Dr. Miller, and the ability to compare to a placebo control.

Solicited symptoms, which include injection site reactions and common general reactions which occur in proximity to the vaccination, were assessed in a diary card subset of nearly 10,000 subjects. There were approximately 5,000 subjects each in the HZ/su and placebo groups.

This slide details the safety endpoints and timeline for follow-up in Zoster-006 and -022. The median duration of the safety follow-up was up to 4.4 years. There were local and general symptoms actively solicited for the first week after vaccinations. These were captured on a subject-completed diary card covering the 7-day period after each vaccination. Cards

were completed only in the subset of approximately 5,000 subjects per group.

In addition, all subjects received a diary card to record unsolicited symptoms for 30 days after vaccination. Subjects were instructed to report any adverse reaction experienced during that time period.

Serious adverse events, or SAEs, regardless of whether they were vaccine related, were collected up to 12 months after vaccination. And furthermore, serious adverse events that were considered related to vaccination by the investigator were captured until the end of the studies, as were all fatalities.

Potentially immune-mediated diseases, or pIMDs, include autoimmune diseases and other inflammatory or neurologic disorders which might or might not have an autoimmune etiology.

Investigators were provided, up front, a specific list of conditions which was developed with external experts and validated with authorities such as FDA. These events were also followed up for the duration of the study. Both new onset and exacerbations of existing pIMDs were captured.

This slide presents the rate of solicited local symptoms of any grade reported during the 7 days following vaccination, which are injection site reactions of pain, redness, and swelling. Injection site reactions were reported more commonly in the HZ/su group than in the placebo group. But as Dr. Didierlaurent mentioned, this vaccine induces a transient

inflammatory process, so this observation was expected. Injection site pain was the most commonly reported local symptom in both groups and age strata.

Local symptoms were reported more frequently in the younger age group, which is why these results have been presented separately here. These reactions were mostly of mild to moderate severity and had a median duration of 3 days in the HZ/su group.

Here now you can see a focus on Grade 3 solicited local symptoms. Grade 3 was defined as redness or swelling greater than 100 mm, or pain which prevented normal activity. These were less frequently reported in both groups, with pain again being the most commonly reported. The Grade 3 local reactions were reported in 8.6% of HZ/su recipients or fewer, and the median duration was of 2 days or less.

This slide presents the solicited general symptoms reported in the diary card subset. As listed from left to right is fatigue, fever, gastrointestinal symptoms, headache, myalgia, and shivering. Fatigue, headache, and myalgia were the most frequently reported symptoms in both groups, with HZ/su group reporting symptoms more frequently than the placebo group. The majority of these reactions were mild to moderate in severity, and the median duration was less than or equal to 2 days in the HZ/su group.

These are the corresponding Grade 3 solicited general

symptoms, and as with the local symptoms, they were reported much less frequently in both groups. Grade 3 fever was defined as a maximum temperature in a 24-hour time period of above 39 degrees Celsius or 102.2 degrees Fahrenheit. For all other general symptoms, Grade 3 was defined as preventing normal activity.

In the HZ/su group, these events were reported in 7.1% of subjects or fewer, with Grade 3 myalgia being the most frequently reported Grade 3 general symptoms in both groups. Grade 3 general reactions had a median duration of 1 day.

So although the solicited symptoms were reported more frequently in the HZ/su than in the placebo group, this finding was not unexpected.

One important question was whether these reactions prevented subjects from receiving the second dose. In both studies, the vast majority of subjects completed the entire series, regardless of treatment group. The compliance rate was greater than 95% in both groups in both studies. Therefore, although the reported weight of vaccine reactions was higher in the HZ/su group, the severity was mostly mild to moderate, the reactions were self-limited in duration, and subjects were willing to take the second dose.

Here we see the incidence of unsolicited symptoms 30 days after each dose. Unlike the previous four slides, this slide includes data from the entire Zoster-006 and -022 populations

and not just the diary card subset.

On the left are events reported within the first 7 days after vaccination, and on the right are reports from the subsequent 23 days. Within the first 7 days we see a similar pattern to the solicited symptoms, with more frequent reporting in HZ/su group and with most events being of mild to moderate severity.

Please note that because the majority of these subjects were not in the diary card subset, we are seeing the solicited symptom reports from the study population that did not receive a diary card to report solicited symptoms.

However, if we look at Day 7 to 29, when the transient effects of vaccination have waned, we see a very comparable rate of unsolicited symptoms reported between the two groups.

Now I will discuss serious adverse events. Serious adverse events were analyzed over a follow-up period of 30 days and 365 days after vaccination and over the entire study period. The rates of serious adverse events were similar between the HZ/su and the placebo group for all time periods analyzed, while a greater proportion of SAEs are reported in the older age group of 70 years and above in both HZ/su and placebo groups.

When we look at fatalities reported by time period and a stratum, we see here, as well, a greater proportion of fatalities reported in the older age group of 70 years and

above of age in both the HZ/su and placebo group. The rates were similar in the HZ/su and placebo group in the 50 to 69 and the 70 years and above group for all time periods analyzed.

Now let's look at the overview of reported pIMDs; pIMDs are potentially immune-mediated diseases that include autoimmune diseases and other inflammatory or neurological disorders which might or might not have an autoimmune etiology.

As previously discussed, investigators were provided a list of pIMDs which was developed and validated in collaboration with external experts; pIMDs were reported at comparable rates regardless of treatment group and age stratum. There was no clustering of reports with vaccination in either group.

Now, coming back to the SAEs, this is a statistical comparison of the 10 most frequently reported serious adverse event terms grouped in system organ classes, or SOCs, within 365 days of vaccination. These terms include infections such as pneumonia, cardiac events, and neoplasm, as would be expected in this population of adults greater than or equal to 50 years of age.

The forest plot shows the point estimate of the relative risk of the HZ/su group divided by the placebo group and gives the 95% confidence interval as well as the p-value on the right-hand side of the graph. The 95% confidence intervals for the relative risk include the value of 1 for 9 out of 10 for

which the p-values were all non-significant.

For vascular disorder, the significance was in favor of HZ/su. The rates of reported SAEs between the two groups in the 1-year follow-up period were similar.

If we would go now a little further, in a way, deeper into the safety data, but by applying the same principles, we would come to the following analysis. The lists you see here are still serious adverse events, but not as they were reported or, as we say in safety, as preferred term and not as a group. The list of preferred terms you see here are the ones reported most commonly, and again, this played as a forest plot. Again, as shown for the system organ class shown previously, all non-significant, all 95% confidence intervals for the relative risk include the value of 1.

It is worth mentioning that by comparing the HZ/su group with placebo, that no medically relevant cluster of serious adverse events were identified in the HZ/su in any time period analyzed.

But in doing a thorough safety analysis in clinical trials, we shouldn't stop here. I will use cerebrovascular accidents as an example of further in-depth analysis for two reasons: first, because of the relevance of all cardio and vascular events specifically in that age group; and second, because it is the one with the lowest p-value even though, strictly speaking, not even close to significance level.

However, I would like to highlight here that cerebrovascular accident was taken as an example only. This analysis is available for any of these preferred terms.

In this table you will recognize the term "cerebrovascular accident" from the previous slide, being the most often reported in the list of terms, which are related to any cerebrovascular event. You see a slight imbalance towards HZ/su for this term, and this for both age groups.

However, you also see the reverse, as indicated by the figures in bold, for other reported terms such as cerebral infarction and ischemic stroke given as a term and more detailed description of the event than cerebrovascular accident.

This graph specifies the time elapsed after the last dose given before the cerebrovascular accident began. Each of those lines presents one case. As you can see, there is no apparent grouping or trend, suggesting that only the natural occurrence of cerebrovascular accident in the elderly population was captured. It is well known that in the general population, cerebrovascular events are common in adults of 70 years and above.

And even more, in the individual case review we have done and are still doing, for all serious adverse events, we found that most of these cerebrovascular events show alternative explanations and risk factors and are unrelated to the vaccine.

A statistical comparison was also performed for the reported rates of specific potentially immune-mediated terms, disease terms, between the HZ/su and the placebo group. This slide illustrates the ratio of relative risk between the reported rate in the HZ/su group divided by the placebo group, again in a forest plot. The 10 most commonly reported events are depicted in this slide.

For these events, all 95% confidence intervals for the relative risk included the value of 1, indicating that the relative risk did not differ between the HZ/su and the placebo group.

Now, given the relevance of the potentially immune-mediated diseases, I would like to present an example of an in-depth analysis done on temporal arteritis. And this was done in a similar way as for cerebrovascular accident.

Why temporal arteritis? This is the one pIMD among this list for which it was not possible to calculate a specific relative risk. So it could be argued that one of the reasons why this one didn't reach statistical significance was that the exposure to HZ/su was not high enough.

However, also here temporal arteritis was taken as an example only. The same analysis exists for any of these potentially immune-mediated diseases.

You see here on the left the three cases of temporal arteritis listed with information regarding country of

occurrence, time between last dose and primary event, and also case-level seriousness. According to this, there is no sign towards a trend of specific time pattern nor regional pattern.

In addition, for two of these cases, plausible explanations regarding etiology were recorded, and this became apparent during the individual case review which was performed, as already described, as the standard.

In the table at the right, you see that within the whole group of vasculitis, which represents a rare event, part of the vasculitis disorder was seen in the placebo group and the other part of them in the HZ/su group. So taken together, also for this preferred term a specific concern, that the higher number seen in the HZ/su group would be related to the vaccine is not justified.

This slide summarizes a few imbalances or cases identified in the HZ/su program that were considered noteworthy by the FDA. These events will be monitored in the proposed pharmacovigilance plan. This table gives information on the three time periods analyzed for the 30-day time period serious adverse events and unsolicited AEs were captured, while in the 365-day time period and the entire study period only SAEs were captured.

A numerical imbalance in the reporting rate of gout and gouty arthritis was observed. These were mostly reported as non-serious adverse events. A biologically plausible

explanation cannot be excluded at this point in time, so gout is considered as adverse event of interest and will be included in the active surveillance activities of the proposed pharmacovigilance plan.

There was one case of lymphadenitis for which FDA assessed the relationship to the vaccine as likely. GSK determined that this might have had an alternative cause. Nonetheless, similar cases which could be summarized as expression of lymphadenopathy will be followed up by pharmacovigilance.

Optic ischemic neuropathy: There has been in total three cases being reported for HZ/su, one being reported as non-serious, while there was none for the placebo group. As a potential consequence of immune-mediated vasculitis such as temporal arteritis, this will be actively monitored.

Amyotrophic lateral sclerosis: Within the 365 days time period, an imbalance of 3 versus 0 was reported. This event will be captured in the active surveillance.

Osteonecrosis: Within the 365 days after vaccination, four cases of osteonecrosis have been reported for the HZ/su group. While all the case descriptions provide alternative explanations such as preexisting osteonecrosis, chronic arthritis, and alcohol abuse, this event will also be actively monitored in the pharmacovigilance plan.

Convulsions: Only in the first 30 days an imbalance towards HZ/su for the convulsion-associated terms was observed

but will be monitored in the active part of the pharmacovigilance plan.

Supraventricular tachycardia: The imbalance seen in the 365 days after vaccination does not appear in a more targeted analysis focusing on all supraventricular arrhythmia. Nevertheless this, as other relevant cardiac events, will be captured in the active surveillance.

After referring here to the proposed pharmacovigilance plan quite often, I would like to give now a more concise description of the plan we are proposing in the following slide.

As a company, we are committed to patient safety, and based on the experience we gained over the years doing pharmacovigilance for vaccines, we plan to continue the proactive and diligent approach that was applied during the clinical development phase.

We will monitor all incoming safety information, which will be mostly spontaneous reports, but also published data, clinical and nonclinical information. This will be summarized and evaluated weekly and/or monthly depending on the kind of data. This approach can be described as standard or routine pharmacovigilance.

In addition, we will further enhance routine pharmacovigilance by putting in place for selected events, notably pIMDs, targeted follow-up procedures in case we learn

of a specific report.

Background rates for adverse events of interest are available to perform specific observed levels expected analysis so we can assess whether the number of events reported exceeds what has been expected, which would highlight a potential concern or a safety signal.

Thirdly, we will further conduct active surveillance by conducting a non-interventional, controlled, prospective cohort study in a large-scale database such as an HMO or electronic medical record.

Endpoints are selected pIMDs, for example, temporal arteritis and polymyalgia rheumatica, and also respective sequelae such as optic complications; also, medically attended adverse events, including serious adverse events.

The follow-up period per subject is aimed to be at least 12 months after vaccination. And this study is currently under discussion with the FDA.

So, to summarize our safety findings, over 17,000 adults received HZ/su during the development program, and more than 14,000 received at least one dose of HZ/su in the two pivotal Phase III safety and efficacy trials, and an approximately equal number of subjects received placebo.

As expected from the known mechanism of action of the AS01 adjuvant system, reactogenicity was more frequent in the HZ/su group, but the majority of the symptoms were mild to moderate

in intensity and of a median duration of less or equal to 3 days.

These reactions did not affect, substantially, compliance for the receipt of the second dose, which was greater than 95% in the HZ/su and placebo groups.

Following the initial 7-day post-vaccination period, the incidence of unsolicited adverse events was comparable between the treatment group from Day 7 through Day 29.

Serious adverse events, fatalities, and potentially immune-mediated diseases were reported at similar rates between the groups and were as expected in an aging population.

No safety concern was identified during the course of HZ/su clinical development. And given the data of the clinical development program, we conclude that the overall safety profile of HZ/su is well characterized and acceptable.

In addition, the safety profile of HZ/su will continue to be actively and diligently monitored in the post-licensure phase.

And now I would like to hand back for a few concluding remarks by Dr. Miller.

DR. MILLER: Thank you, Dr. Stegmann.

It's now my pleasure on behalf of GSK and the zoster team to summarize the conclusions of our clinical development program.

The U.S. experience is more than 1 million cases of herpes

zoster each year, and the lifetime risk of herpes zoster in the U.S. is one in three adults, which increases to 50% in those of us reaching our 85th birthday.

The most important risk factors for this disease are increasing age and immunosuppression. The risk for postherpetic neuralgia also increases with age and has an overall incidence of 10 to 30% in herpes zoster patients.

Current treatment and management options for herpes zoster are suboptimal in terms of effectiveness, and the currently licensed vaccine provides incomplete protection, so an unmet medical need remains for a more efficacious vaccine.

HZ/su is a combination of the gE antigen and the AS01B adjuvant. The glycoprotein E antigen was chosen for its effectiveness as a T and B cell antigen. AS01B was added to enhance the immune responses, particularly in terms of restoring cellular immunity. The excellent clinical results demonstrate that the strategy of combining a single inactivated protein and an adjuvant results in effective control of herpes zoster.

HZ/su demonstrated high and durable efficacy. Vaccine efficacy against herpes zoster was 97.2% in adults greater than or equal to 50 and 91.3% in those greater than or equal to 70 years of age.

In addition, we observed 88.8% efficacy in preventing PHN in adults greater than or equal to 70. In those greater than

or equal to 50, the efficacy was 91.2% against PHN. And there were no cases of PHN in those aged 50 to 69 years in the HZ/su group.

The efficacy in preventing herpes zoster was consistent across age strata and persisted for at least 4 years.

We've also demonstrated that HZ/su has an acceptable safety profile. This vaccine has been thoroughly evaluated in more than 17,000 subjects across the clinical development program and more than 14,000 subjects in Zoster-006 and -022. Local and systemic symptoms within 7 days of vaccination were more frequently reported in HZ/su, but the majority of symptoms were mild to moderate in severity and of self-limited duration. Serious adverse events, fatalities, and potentially immune-mediated diseases were reported at similar rates between the groups regardless of time periods considered, and GSK will continue to perform active surveillance in the post-licensure period.

Given the high and sustained vaccine efficacy against herpes zoster in all age strata and the acceptable safety profile, we conclude that the benefit-risk profile of HZ/su is favorable.

And to recap, our proposed indication is for the prevention of herpes zoster, or shingles, in adults 50 years of age or older. By preventing herpes zoster, HZ/su also reduces the overall incidence of postherpetic neuralgia.

Shingrix is expected to provide substantial health benefit to individuals greater than or equal to 50 years of age.

And thank you very much for your attention. This concludes our presentation.

DR. EDWARDS: Thank you very much, Dr. Miller.

Other questions? Yes, Sheldon.

MR. TOUBMAN: Before my sets of questions, I should explain that I am the one complete non-expert here, so I'm a layperson, and so you have to answer my questions from that point of view.

DR. EDWARDS: You're a very important part of the Committee.

MR. TOUBMAN: Thank you.

My first set of questions concerns a safety issue not even discussed anywhere in the documents, and that is that I noticed this is a recombinant product, and so I have a series of questions related to that.

The first is why was a recombinant product used? Is that unusual? Others on the Committee might know the answer to that, whether you're seeing it a lot, but I'd like to know what the frequency is. Have any studies been done related to that aspect, that it's a recombinant product, either by looking at this product or similar products in terms of longitudinally the risks, the safety risks associated with using a recombinant product?

And, also, a last question in that group is the relevance of the fact that it's not a live virus, the fact that it's -- whereas the current product out there is a live product, again, relevant to the fact that it's recombinant.

And then my other questions are about persistence. The current --

DR. EDWARDS: Perhaps --

MR. TOUBMAN: Sorry.

DR. EDWARDS: -- you'd like to answer --

MR. TOUBMAN: Oh, I'm sorry.

DR. EDWARDS: -- one question at a time. Sometimes I forget.

MR. TOUBMAN: Okay.

DR. EDWARDS: I have too many. So perhaps Dr. Miller would -- so the first one is in regards to the recombinant.

DR. MILLER: Yes. And I'm going to ask someone from our preclinical group also to come and speak to the formulation of the vaccine, but I will tell you that recombinant products actually are in other licensed vaccines. So, for example, the hepatitis B vaccine, which is also used in this population and has been licensed at least since the late '80s is a recombinant hepatitis B surface antigen.

We chose the glycoprotein E antigen with the adjuvant combination specifically because we wanted this vaccine to be able to address needs in individuals who could not receive live

viral vaccines. So there currently is a parallel ongoing development program in those who are immunocompromised for whom it would not be safe to receive a live attenuated vaccine.

And Dr. Didierlaurent is going to come up and make a few further comments to your question.

DR. DIDIERLAURENT: Dr. Didierlaurent, Adjuvant Platform, GSK.

So gE is produced in natural cells, and this is a fairly classical approach to produce therapeutics. And we are also producing -- I mean, we have vaccines in development with recombinant antigens, so for us, this is a very common approach that we used in the company.

DR. EDWARDS: Please, go on.

MR. TOUBMAN: Well, but the question -- thank you for answering that, but the question I had further was what safety analysis has been done using a recombinant product either here or otherwise in terms of over time what risk we might see, all kinds of risks that we just don't know about? What has been done there?

DR. MILLER: Well, so to answer your question, the safety analyses are the ones that we do for any vaccine. So before vaccines would go into human clinical trials, we conduct preclinical safety and toxicology experiments, and then the safety experiments that we do are the comparisons that we've made to the control group in this case. And maybe you can give

me some idea of what additional data you're looking for and then I can determine who could answer your question.

MR. TOUBMAN: Well, one question might be carcinogenicity, however that's properly pronounced, so is there a cancer risk over 5 or 10 years? You know, has that been looked at?

DR. MILLER: So I'm going to ask Dr. Stegmann from our safety group to come and speak to your question.

DR. STEGMANN: Jens Stegmann, Clinical Safety/Pharmacovigilance.

And as already outlined by my colleagues, so this is a quite -- this is a rather common approach for producing vaccines. And as you were specifically asking for carcinogenicity and as being known for other products using a similar approach, if that would have been occurred in this development program, we would have picked it up in the long-term safety data we are collecting as well, and we are going to continue to collect. So far we don't have any indication that for other vaccines, and Dr. Miller gave an example, as well for these, that there is a higher risk that patients could develop cancer after vaccination for that.

MR. TOUBMAN: Thank you. And my last question. Thank you very much. The current vaccine, the data show that by Years 8 to 11, it really has no greater effectiveness than people who are not vaccinated, so we see the obvious need there. But there was mention of possible booster vaccines; I don't know

how common that is for the current vaccine.

My question is with regard to this product, the data, the best data we have is 6 years out. How do we know that this product wouldn't have a similar, at 8 to 11 years, say, a similar lack of improved effectiveness? What is there to base that on?

DR. MILLER: So your question is exactly the reason we continue to extend both our early development studies, so we have some 9-year persistence data, so a continuation of the Zoster-003 study has recently become available for 9 years. Those data were not available in the original BLA, and that's why I didn't include them in the core presentation. They have been presented, however, at the ACIP, so I'll show you them here.

And, again, these are the same subjects in the antigen dose ranging study. These subjects have now, beyond the Zoster-024 6-year persistence time point, been followed out to 9 years, and again, you see the cell-mediated immunity on the left and you see the humoral response on the right, and we see that the plateau continues to be maintained.

We have used these data to model, in using three different statistical models, how long we might expect persistence to last. Our current modeling estimates are out to 15 years. But as you rightly point out, real-life experience is incredibly important, and that's why we continue to extend the follow-up

of the subjects in the Phase III studies for efficacy.

We will look at boosting in these subjects with HZ/su, both in a continuation of the Zoster-060 study -- it's actually ongoing now at Year 10 persistence, to see the immune impact of giving additional dose, and then we will also look at boosting in the long-term efficacy trials, again, at 10 years post-vaccination.

MR. TOUBMAN: Thank you very much.

DR. EDWARDS: Good questions.

Dr. Long.

DR. LONG: I have a few questions. The first is, is the response with the adjuvant, just talking about the adjuvant now, does it simulate a natural response as in varicella, or is it different? Is it spiked to be a different way to cell-mediated immunity or antigen-presenting cells?

DR. MILLER: So Dr. Didierlaurent is going to come and speak to your question about the nature of the AS01 response.

DR. DIDIERLAURENT: Dr. Didierlaurent, Adjuvant Platform, GSK.

So you're asking about difference with the virion infection itself, is what you were saying?

DR. LONG: Yes, yes.

DR. DIDIERLAURENT: So let me just address what do we know about AS01, and then I'll comment on the comparison.

So we have seen that the MPL target TLR-4s, toll-like

receptor 4, which is a natural receptor that is used to detect infection, and also the quintessential one is triggering the pathway to caspase-1, which has also been involved in detecting natural response. So these are pathways that are used by the host to detect pathogens.

As far as how this is different from the varicella infection, the problem with this is that most of the animal models where we could actually analyze pathways are not the vaccine -- sorry, the virus does not replicate in these models, so it's very hard to address your question. However, since it is a virus, very likely the receptors will likely be different.

DR. LONG: Because as, I'm sure you know, strikingly in pediatrics, varicella was associated with an increased risk of stroke in the next 6 months. So the example that you used to show us more about safety about cerebrovascular accidents is really an important one about biologic plausibility as that could be a vasculitis inflammatory response.

Was there any time relationship in the 365 days of those grouping of cerebrovascular accidents following vaccination?

DR. MILLER: So Dr. Stegmann is going to return to discuss the safety analyses.

DR. LONG: You may have said that. I may have missed it.

DR. STEGMANN: Jens Stegmann, Clinical Safety/Pharmacovigilance.

And the answer is no, there is no specific time pattern

related to the vaccination for those events.

DR. LONG: And then the last biggest question I think I have, I think I calculate that probably 2,000 United States residents received this vaccine in total; is that about correct?

DR. MILLER: That's about correct, yes.

DR. LONG: And so then I want to know exactly how they were recruited. Eighty percent had one comorbidity. How many had multiple comorbidities? To try to answer the question, did we have a group that was enriched or less rich for maybe stroke, if we were interested in stroke, for instance, obesity and diabetes and hypertension and all of those things?

DR. MILLER: So I think I heard a few questions in there, and maybe I'll repeat them --

DR. LONG: Yes.

DR. MILLER: -- back to you to be sure that I captured it correctly. So the first was really around the patient recruitment and to discuss how we recruited the subjects. So in the U.S., they were recruited the same way as they were recruited outside of the U.S. The inclusion/exclusion criteria were designed to ensure that the trial would be safe enough for the subjects who were participating, and what I mean by that is while we had preclinical safety data, toxicology data.

And the early clinical data before entering into these trials, it was really the first time that we were enrolling

such a large cohort, and so there were some exclusions in terms of making sure that subjects, for example, were expected to have a life expectancy of 4 years so that they could complete the efficacy follow-up in the trial. Certain immune-modulating medications were excluded, and that was because we have, again, the parallel development program in the special population of immunocompromised individuals. But by and large, adults were allowed into the trial with their comorbid conditions.

And let me show you a post hoc exploratory analysis that was done on the subjects with comorbid conditions. It's a complicated slide with a lot of information, so I'd like to take you through it slowly, although I'll tell you that the main message in the end was that we looked at the efficacy of the vaccine in subjects with various comorbid conditions and found the results to be very comparable to the results of the main study.

What you see on the left-hand side of the graph are various baseline conditions, and these are the most commonly reported baseline conditions when we ascertained a medical history upon entry into the trial.

In orange, big *N*, you see the numbers of subjects reporting these comorbid conditions in the HZ/su group and then in gray for the placebo group. And while they're well balanced between groups, while we don't have, for example, stroke on this list, it wasn't one of the most commonly reported

preexisting conditions. We do have, for example, hypertension, hypercholesterolemia, and in here we're looking in the thousands of subjects. And when we looked, again, at efficacy across those populations, we saw estimates that are very similar to the overall compilation.

DR. LONG: And do I remember, then, that that's about 14,000? These numbers are of 14,000?

DR. MILLER: Yes. So these numbers would be -- if we take, for example, the arthritis, osteoarthritis in the first line, it means that there would be approximately 5,000 in the HZ/su group over 14,500 subjects total that reported that condition.

DR. LONG: Obesity wasn't in the comorbid possibilities?

DR. MILLER: I'm going to invite Dr. Oostvogels, who is the clinician actually in charge of the trial, to speak to specifically how obesity was captured.

DR. OOSTVOGELS: Lidia Oostvogels from the clinical team.

Actually, obesity was also one of the comorbidities that was captured; however, here on the list that Dr. Miller has put up, we have now shown the comorbidities that were most common. However, specifically, in the U.S. population, conditions like higher cholesterol, obesity, diabetes were even more prevalent than in the overall population.

DR. LONG: It is remarkable that there are very few African American and Hispanics in the group, so I guess, just

trying to understand this is requesting -- does it support the use of the vaccine in adults 50 years of age and older? I'm trying to understand how healthy or unhealthy or similar to the United States population these very few people are.

DR. MILLER: Maybe we could put back up the slide from the core deck showing the demography in the total group, as well as in the North American group, because I think it will help me address your question. But while the slide's being called up, maybe to start by saying --

DR. OOSTVOGELS: It's C-6.

DR. LONG: CE-6, I think, is what I was looking at.

DR. MILLER: So we remain committed to increasing the inclusiveness and diversity in our clinical trials, and admittedly, this is a newer population for us. We're working as we go to work with additional investigators that can recruit these patients.

But I did want to point out that when we enroll a trial globally, and we've done that actually to increase the generalizability, not just in the U.S. but also in other countries that have interest in the vaccine, some of the reported rates are a bit diluted out.

So when we looked at the U.S. and Canada, for example, the African Americans are more reflected. And if we looked in the U.S. population alone, actually, the number increased to about 8%, so getting at least a little bit closer to the general

population. But these are the subjects that we enrolled in the study and on which we have to base our assessment.

DR. LONG: Their actual numbers, though, are extremely low, African Americans and Hispanics.

DR. MILLER: Yes. Although I will point out that from a Hispanic perspective, a number of Latin American countries were included, and so while there were not American Hispanics, there were Hispanics included in the trial. And that's why the global population has a higher rate of Hispanics, about 10%.

DR. EDWARDS: Holly.

DR. JANES: Thank you. I have several questions. Would you let me know if we should defer some for the afternoon?

So one following up on Sarah's question: So are there data, understanding the public health needs based on the earlier presentations this morning, are there any data on safety or immunogenicity in the immunocompromised population?

DR. MILLER: So as part of our initial file, there was a safety and immunogenicity study in subjects who had hematopoietic stem cell transplants, and then there was a second study in subjects who were HIV positive.

In addition, we have ongoing studies in patients who have solid organ tumors and are receiving chemotherapy, patients who have hematologic malignancies and are receiving chemotherapy, and then renal transplant patients, so post-transplant. And maybe it actually helps if I show you the development program

that we have ongoing.

So what we have available for the moment and as part of the BLA are the studies on the left, so Phase I to II. These were conducted in adults greater than or equal to 18 years of age, and again, those were the stem cell transplant patients and the HIV-infected adults.

In our Phase III program, we have an ongoing efficacy study in stem cell transplant patients, and we are awaiting those results in the coming months.

And then the other subpopulations I mentioned, the two populations of individuals with cancer, so solid organ tumors and hematologic malignancies and the renal transplant patients.

And then should these results indicate that it is advisable to move forward, we have a pediatric plan in renal transplant patients and patients with solid organ and hematologic malignancies.

DR. JANES: Okay. And then a question about the efficacy analyses and the primary endpoint analyses of efficacy in the efficacy trials that you presented today: So I noted that the primary analyses of efficacy have all been done in what you would refer to as the modified total vaccinated cohort, which is not all randomized and enrolled participants but rather the subset who were still at risk for the zoster's endpoint, I think, within -- after 2 months post-Dose 2 and importantly also including only participants who received both doses of

vaccine.

So can you help us understand the fraction of the population that were excluded from those efficacy analyses, whether that was imbalanced between the two arms, you know, both in number and in characteristics and whether you have estimates of efficacy in the entire randomized population?

DR. MILLER: Yes. So the numbers of subjects that were excluded from both groups were comparable between the two groups. I can show you the study cohorts first, just to depict how we moved from one cohort to the next.

So as you mentioned, the efficacy analyses were performed in the middle column, the modified total vaccinated cohort. These were the subjects who received two doses, and their inclusion in the cohort started once they reached 30 days post-Dose 2.

And I can also show you next the progression between the HZ/su group and the placebo group from the total vaccinated cohort to the modified total vaccinated cohort. This is from the Zoster-006 study, but the results are also similar in the -022 study.

And as you can see, in both groups, the most common reason why individuals did not continue -- well, actually, it was different between the two groups. In the placebo group it was more commonly because they had herpes zoster before Day 30, but typically it's errors in terms of receiving either the wrong

vaccine or they're not vaccinated according to the schedule we requested they be vaccinated to.

And then you had also asked me whether we have efficacy estimates in the total vaccinated cohort; we did do that as one of our secondary analyses, and the results were comparable with the initial analysis.

And so what I have here are the results from the pooled analysis in the subjects greater than or equal to 70 years of age. We have the same data available for those 50 years of age and older, and again, the results are not substantially different from what was seen in the -006 study. Here you see vaccine efficacy estimate of 89.9% in the total vaccinated cohort; that's compared to 91.3% in the modified total vaccinated cohort.

And I can also show you the estimate in the total vaccinated cohort from Zoster-006. Here we have 95.8% efficacy, and that's compared to 97.2% in the modified total vaccinated cohort.

DR. EDWARDS: Dr. Sawyer.

DR. SAWYER: I'm interested in exploring your calculation that this needs to be a two-dose vaccine. In recent years we've had a number of vaccines licensed as multiple doses and then subsequently reduced the number of doses needed.

In the background material we received, we see that both cell-mediated immunity and antibody levels are certainly higher

with two doses, but with one dose they seem to plateau at a level above the baseline. So do we know what threshold is required to really lead to protection? And as an extension of the previous question, do you have vaccine effectiveness data with just the 700 or so people who got just one dose?

DR. MILLER: So, to answer your first question, there is no well-established correlative protection to define what would need to be achieved. And as Dr. Didierlaurent showed you, you're correct, we saw not only that the peak was higher with two doses, but importantly that the persistence was higher with two doses.

And as we were making our decisions about how to study this vaccine in the further efficacy trials, we wanted to be sure that when we vaccinated individuals, especially those individuals who are younger, we were going to have an immunogenicity that would persist over time since they would need to be covered throughout a longer period of life, again, zoster reactivation.

Your second question was around whether we looked at one-dose efficacy and while this analysis is not as robust as what we see in the two-dose, because the study was designed for two-dose efficacy, we did perform the analysis, and we saw that there was efficacy with a single dose.

I need to highlight that the analysis is limited by the fact that there was high compliance in both groups, so 95% of

subjects received two doses in the Phase III trials, and therefore, most of these subjects, either they were part of the 5% that didn't receive a second dose or these were individuals who had their case of herpes zoster occur prior to Day 30 post-Dose 2, and therefore the average follow-up for an individual was only about 80 days post-vaccination, so sample size and duration of follow-up are limited.

Nonetheless, if you look in the top row, that's analogous to the Zoster-006 analysis in those greater than or equal to 50; one-dose efficacy was 90.8%. And in the pooled analysis for those greater than or equal to 70, that's at the bottom row of the table, the one-dose efficacy was 69.5%.

DR. EDWARDS: Dr. Wharton.

DR. WHARTON: I'd like to go back to Slide CS-16. And it looks to me, from looking at this graph, like there are more events in both the vaccinated group and in potentially the placebo group as well, in the first 90 days compared to later in the period, and I was trying to think through where the -- how the events are allocated based on receiving the first or second dose.

Would the way this work is if a person received both doses, as the vast majority of the people in the study did, that the -- any events occurring between the first and the second dose would be allocated in the first couple of months, and then after the second dose, those events -- only those

events could be later on in this 365 days of observation?

DR. MILLER: So the way that the safety data were analyzed, actually, Dr. Stegmann will address that question, so Dr. Stegmann.

DR. STEGMANN: Jens Stegmann, Clinical Safety/Pharmacovigilance.

The way these data were captured, that events were counted after any dose given, so these -- for the second dose, predominantly you find on the later time period on this graph that's been done. As you were suggesting that there might be an accumulation in the first 90 days in the HZ/su group, this is not the case. We checked for that, and there's not a specific pattern regarding that.

DR. EDWARDS: Hana.

DR. EL SAHLY: I wonder if, in the breakthrough zoster cases, did you go back and look at the cell-mediated immunity and humoral immunity to find a cutoff that seemed beyond which the risk increases of getting zoster?

DR. MILLER: So an exploratory endpoint of our trial was, indeed, to look for a correlate of protection. I should say that this analysis was not available at the time that the file was submitted, the FDA has not been able to review it in detail and therefore it hasn't been validated by them, so I won't talk too much into detail in that analysis today.

I will say that we did look at the humoral immunity in

those who had breakthrough cases. For cell-mediated immunity, because sites are more specialized to be able to conduct that analysis, so they have to be able to acquire and process the peripheral blood mononuclear cells in a very rapid time frame, we had only three sites that did that and unfortunately, or fortunately for those patients, the breakthrough cases did not occur in the subjects who had CMI.

So we did have 32 breakthrough cases in the HZ/su group overall in the modified total vaccinated cohort. There were three subjects who failed to achieve a vaccine response, and that was defined as a fourfold rise in titer.

In Zoster-006, there was no apparent trend between pre- and post-vaccinations, and in Zoster-022, in these subjects there was a trend towards lower post-vaccination concentration, so in the older subjects who had the breakthrough disease. But this is really limited by the fact that the number of breakthrough cases was quite small in both of the studies.

DR. EL SAHLY: Okay. Was being on prednisone or other minor immune-compromising medication or condition an exclusion criterion?

DR. MILLER: So being on prednisone at a defined level and for a defined time period was an exclusion criterion. So if you had taken prednisone overnight because you thought you had a poison ivy rash, that would not be someone who would be excluded, but someone who is on prednisone longer term for

treatment of a chronic condition was an exclusion criterion.

And, again, those subjects will really be better studied in the immunocompromised clinical development program so they'll be captured in those who are receiving cancer chemotherapy and also the renal transplant patients.

DR. EDWARDS: Dr. Englund.

DR. ENGLUND: Yeah, sorry. I would like to go back to the CVAs post-vaccination, which was CS-16, which is a safety event. So my question is, and not being a statistician, but concerned about some of the CVA issues. Since day zero on both of these is from either vaccine, I don't see any statistical analysis here. But my question is, in the first 90 days or 120 days, is there a statistical difference between the number of subjects reporting the event in the vaccine versus the placebo group?

DR. STEGMANN: So as I explained, this is a specific time to onset description of cerebrovascular accident. What we have done in order just to further look into whether there is a specific risk for cerebrovascular events in total, so what I can share with you is these analyses we have done by standard MedDRA queries where we compared for the time period.

Since you were asking for 90 days, I have it here for 30 days, as to whether either ischemic or hemorrhagic cerebrovascular events do occur more often in the HZ/su group, and as you can see, for the 30 days, it's even -- well, based

on a relative number, it's the other way around, as well for 365 days, that we don't see any relevance, a difference, with the occurrence of these events.

DR. ENGLUND: So maybe I should refer to my statistical colleague across there. I'm just used to seeing things presented more as a time-to-event analysis than just the simple graph that you've shown me, so that's -- perhaps you could address that. And Holly, if I'm out to lunch, tell me.

DR. JANES: In my experience, it is common to capture safety endpoints without the time information, given that, you know -- yeah, so capturing them within a fixed time period post-vaccination is common, although I don't, as you suggest, see the analysis out to 90 days post-vaccination. I don't know if you have more analyses to show on that particular point.

DR. STEGMANN: We don't. For the 90 days, we don't have that specific analysis for that, and we have looked into the relevant time period of 30 days after each vaccination, and as I just explained, for cerebrovascular events as here, we have to see as to whether we can provide that information still in time of the -- just looking into the 90 days for -- and then I would suggest, for the major cerebrovascular events as being in the standard MedDRA vary because this combines.

Because the argument I was trying to make is that the preferred term "cerebrovascular accidents" might not be inclusive of the relevant event we are capturing because it's

just one -- as shown, one event or description out of a list of a number of those, so that we would like to combine it -- as it's being standard.

DR. EDWARDS: Karen.

DR. KOTLOFF: Yes, I wanted to go back and look at Slide CS-19 and just get some clarification on the events of special interest. So there were some that had an imbalance between the treatment and placebo group, for example, gout and possibly convulsions and possibly supraventricular tachycardia.

And I'm wondering if you had any data on whether there was preexisting disease, for example, for either previous seizures, previous gout, whether the preexisting uric acid was elevated or whether these were completely new onset conditions post-vaccination.

DR. MILLER: My colleague, Dr. Stegmann, is already here to address the question.

DR. STEGMANN: Okay, Jens Stegmann, Clinical Safety/Pharmacovigilance.

I've heard two concepts you're interested, the one is gout and the other one was --

DR. KOTLOFF: Convulsions and SVT.

DR. STEGMANN: Maybe we should start with gout and gouty arthritis. What I can show to you is that by comparing HZ/su with placebo, among those that risk factors were existing, it is for those cases, and I highlighted -- you highlighted, was

numerical imbalances that there was for the high proportion, if not all risk factors for gout being described. And then you see the different phases between new onset and flare, so the reoccurrence of that gout and symptoms. So this regarding gout.

And for the other concept, convulsions associated terms, I would like to present the individual case description we have for those events. It's a rather busy slide, so I would like to guide you through that, and what you can see is, for example, that the first case is being described as actually questionable, whether this is real convulsions or convulsions associated terms, but it was, in a way, received as such.

For the seizure cases among this list we have, so we have a high proportion or at least two for which we have confounding factors already known or alternative explanation as being seen. And you see that here that there is a history of epilepsy and ischemic strokes as well -- this is actually two times, and one was an aneurysm being assessed by MR. So there is for this, we are arguing here on low numbers, a high proportion with alternative explanations or with gout.

DR. KOTLOFF: And that supraventricular tachycardia?

DR. STEGMANN: Supraventricular tachycardia, the numerical imbalance we have seen by doing a further analysis into that -- and I will show to you here the analysis for supraventricular tachycardia associated term because, again, as we have

discussed it for cerebrovascular accident, that might not be that specificity for the term.

And you see here that supraventricular tachycardia, yes, is a numerical imbalance towards HZ/su. But when you look at the associated terms, which also are captured in a standard MedDRA query, you'll see that the numerical imbalances does not persist. So in the context of the related terms for that, this numerical imbalance does not still occur.

DR. MILLER: Thank you, Dr. Stegmann.

Maybe one final point to make about the patients with gout that I believe Dr. Stegmann meant to mention was that all of the patients that reported gout in our trial, except for one, had a preexisting risk factor, so they either previously had gout or had some other risk factor.

DR. EDWARDS: I had a couple of questions. First of all, did the immune responses at all correlate with the severity of the local reactions? Did it suggest that with more local reactions you might have had more inflammatory response and a higher CTL response or immune response? Were correlations made with that?

DR. MILLER: So we did attempt to do that analysis; it turned out to be quite a complicated analysis to perform. We did see, at a population level, that higher levels of reactogenicity correlated with higher levels of immunogenicity, but to then take that to an individual level and say an

individual patient who would have a reaction would have a specific immune response, that's not a correlation we're able to make.

DR. EDWARDS: And certainly this wasn't a part of your study, but were there any individuals who had been inadvertently given the other vaccine that then got boosted with your vaccine? Were there any of those responses to sort of get to some of what Mark was perhaps thinking about?

DR. MILLER: Yeah. So maybe a better way for me to address that -- there were a few patients in the trial where that happened, but we actually studied the previous administration of Zostavax and then subsequent administration of HZ/su. Again, this was a trial that was not included in the initial BLA and that's why it hasn't been covered in the briefing document nor in the presentation, but it is something we know that people will be interested in reviewing.

So we did do this revaccination study. It was reviewed at the ACIP in June, and this is a study where approximately 215 individuals who had previous documented Zostavax and then 215 individuals who were previously unvaccinated were given two doses of HZ/su at 0 and 2 months. Immunogenicity follow-up was performed at prior to vaccination, 1 month after the first dose, and then 1 month after the second dose, with a follow-up visit at Month 12. The data are currently available for Month 3.

And what I can say is that the study met its primary objective, which was to demonstrate non-inferiority in terms of the geometric mean antibody concentrations. And so here you see the top line data from that study, so the GMC ratio was 1.04 with an upper limit of 1.17, and that was lower than the predefined statistical criterion of 1.5.

DR. EDWARDS: Thank you. And then just a final comment: The guinea pig model might be utilized to actually look at your question to whether how -- that's Sarah's question, actually, and perhaps for future days.

DR. MILLER: Thank you for your suggestion.

DR. EDWARDS: Questions?

Sarah.

DR. LONG: Just a follow-up on this study. Since 25% of the population, by statistics, if they're still alive, will have received this live attenuated vaccine, we're going to have to understand if the license will include or exclude those individuals, so we really are also interested in safety data in that group.

DR. MILLER: Sure.

DR. LONG: Do you have any information?

DR. MILLER: Yes, there is information. And the reported reactions were comparable to what was seen in the Phase III study, and that's in terms of the local and general solicited symptoms. I'll also show you the comparison of the SAEs, the

unsolicited AEs, and the unsolicited related AEs. And, again, because there are multiple data points, let me take you through the slide.

In gray we have the subjects who received Zostavax previously. In green we have those who did not previously receive zoster vaccine. For the SAEs and the related unsolicited AEs, the groups were well balanced. There was a higher reported rate of unsolicited AEs in the previously vaccinated group, but the 95% confidence intervals overlap. And may I please have the slide with the specific reactions?

(Pause.)

DR. MILLER: Yes, there we go. So, to show you what the unsolicited AEs looked like by system organ class, so you see again, in orange, the previously vaccinated; in gray, those not previously vaccinated. And while there were some categories more commonly reported in the previously vaccinated group, there were also some categories more commonly reported in the not previously vaccinated group.

DR. EDWARDS: Thank you.

Any other final questions?

Yes, David.

DR. GREENBERG: Thank you. I'd like to ask a question about the immunogenicity. I'm sorry, the efficacy. So I'm looking at CE-8 and 9. Particularly, CE-9 shows the data for those who are 70 years of age and older, and it's the pooled

data from the two efficacy trials, and I'm wondering if you could share with us the data, efficacy data, specifically for Trial 022, those 70 and over, but that study alone, since primary outcome was for the efficacy?

DR. MILLER: Yes, so here are the data from the Zoster-022 study alone. The vaccine efficacy in those greater than or equal to 70 was 89.8%. Again, similar to that in the pooled dataset, we saw consistent efficacy in those 70 to 79 and greater than or equal to 80, so 89 to 90% in both age cohorts.

And I should mention that the primary endpoint for this study had to be met prior to being able to pool the data and show the more robust efficacy estimate on the larger dataset.

DR. GREENBERG: Thank you. And I'd also like to ask, in the safety section, you provided to us the median duration of both the injection site and systemic reactions and those for Grade 3, and as you pointed out, they were generally quite low medians of less than 3 days or less than 2 days.

Could you give us some sense as to either a range or what proportion might have had overall symptoms or Grade 3 symptoms beyond, say, you know, 6 or 7 days?

DR. MILLER: Yes, we did perform that analysis, and it was a small, as you mentioned, proportion of the overall total. So here are the solicited symptoms that were ongoing beyond the 7-day post-vaccination period.

So in Zoster-006, less than 10% of them were ongoing

beyond 7 days in the HZ/su group, and the general symptoms had a lower duration rate, so about 1 to 5% were beyond 7 days. The median duration of those subjects that were beyond 7 days was between 9 and 11 days. And importantly, the same trend was observed in the placebo group and in the Zoster-022 study.

And what we saw, when we looked at these, was although the reactions were more commonly reported very proximal to vaccination in the HZ/su group, once you got beyond vaccination, the rates actually were quite comparable between the placebo and the HZ/su group.

DR. GREENBERG: Could I ask one final question --

DR. EDWARDS: One more.

DR. GREENBERG: -- before lunch?

CS-9 reviews the unsolicited AEs within 30 days post-vaccination. There are some differences there between the vaccine and placebo groups, if I'm reading that right, on the left-hand side for that early period of days 0 through 6. And I'm just wondering if either breakdown of those by system organ class or perhaps those that were classified as adverse reactions versus adverse events could help us understand the differences between the vaccine and the placebo groups.

DR. MILLER: So I maybe want to clarify a point that was made, but I think a lot of points were made, so it may have been a bit lost. In this analysis, unlike for the solicited symptoms, the solicited symptoms were captured in a diary card

subset, so approximately 10,000 subjects, in addition to a diary card to write down any reaction that occurred, had a specific diary card where they were prompted to enter symptoms for a number of days post-vaccination. When we looked at the unsolicited symptoms over 30 days, that was done in the entire population, so 14,000 subjects in each group.

What we see in day 0 to 6 is that the commonly reported reactions are really similar to those we look for in the diary card, so constitutional symptoms and symptoms at the injection site. If you take that first 6 days out where we know that the local and systemic reactions are more commonly reported in the HZ/su group, what you see in Day 7 to 49 are very comparable rates between the groups, and the specific terms were comparable as well.

DR. EDWARDS: Okay, thank you very much.

We will now break for lunch. We will come back at 12:30 so that we can keep the time frame, and so we'll be slightly truncated, but we can all eat quickly. Thank you.

(Whereupon, at 11:49 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:30 p.m.)

DR. EDWARDS: Dr. Agger will begin.

DR. AGGER: Good afternoon, everyone. I'm Paula Agger. I am a medical officer in the Office of Vaccines Research and Review, CBER/FDA. I, along with my colleague, Dr. Rebecca Reindel, was responsible for the clinical review of the data submitted by GlaxoSmithKline in support of the licensing application for Shingrix.

In this presentation, I will highlight some background information, provide an overview of select clinical studies submitted to the BLA, discuss the efficacy and safety data from the clinical endpoint studies, followed by select efficacy and safety data from the pooled analysis of the pivotal studies. Finally, a brief summary will be presented.

This slide reminds you that Shingrix consists of 50 µg of recombinant varicella zoster virus glycoprotein E lyophilized and presented in a single dose vial. It's mixed with 50 µg of the AS01B adjuvant and administered as a single 0.5 mL injection at Months 0 and 2.

The Applicant's proposed indication is presented here. Since it's been presented at least twice before, I will skip this slide.

The Applicant submitted two clinical endpoint studies to the BLA: Zoster-006 and Zoster-022. Both were Phase III,

randomized, observer-blind, placebo-controlled, multicenter clinical trials to assess the prophylactic efficacy, safety, and immunogenicity of Shingrix when administered IM on a Month 0 and 2 schedule. Zoster-006 enrolled subjects 50 years of age and older, and Zoster-022 enrolled subjects 70 years of age and older.

The next two slides delineate additional studies that were among those submitted to the BLA. Zoster-004 supported concomitant administration of Shingrix and quadrivalent influenza vaccine. Zoster-026 confirmed that the humoral immune responses to Shingrix administered at Months 0 and 6 were non-inferior to that when Shingrix was administered at Months 0 and 2.

Zoster-032 provided data to support the intramuscular rather than the subcutaneous route of the administration of the vaccine. Zoster-033 was a one-arm, uncontrolled non-IND study of the safety and immunogenicity of Shingrix when administered IM at Months 0 and 2 to 96 subjects with prior physician-diagnosed HZ. These subjects were followed for 12 months after Dose 2. In the study, six study subjects reported nine unconfirmed cases of HZ during the study. The Applicant has proposed a more robust evaluation of Shingrix in this population.

To begin our discussion of the clinical endpoint studies, Zoster-006 and -022, I'd like to remind you that they had the

same primary objective, primary endpoint, and analysis plan for the primary endpoint.

The primary objectives were to evaluate Shingrix vaccine efficacy in the prevention of herpes zoster as compared to placebo as measured by the reduction in HZ risk. The primary endpoints were confirmed HZ cases during the study. The analyses of the herpes zoster primary efficacy endpoint evaluated the reduction in HZ risk stratified by age and region, considering the total number of HZ cases observed and time at risk.

Select secondary objectives common to both studies included the evaluation of vaccine efficacy in the prevention of overall PHN. In subjects with confirmed HZ, select secondary objectives included evaluation of vaccine efficacy in the reduction of duration of severe worst herpes zoster pain, reduction of herpes zoster-related complications, hospitalizations and mortality, and reductions in the use of pain medication. Shingrix safety and reactogenicity were also secondary objectives. Immune responses to Shingrix vaccination and the persistence of immune response were exploratory objectives but will not be discussed in this presentation.

Common study design elements for Zoster-006 and 022 were as follows: Both studies were conducted in parallel at the same sites in 18 countries. Both enrolled subjects without prior HZ or prior vaccination against varicella zoster virus or

HZ. They enrolled subjects without immunodeficiency or immunosuppression, and in both studies, subjects were randomized 1:1 to receive Shingrix or placebo at Months 0 and 2. Subjects greater than or equal to 70 years of age were randomized to one of the studies prior to randomization to a treatment group.

There were six study visits, two of which, at Months 0 and 2, were the vaccination visits, and one end-of-study contact. There were monthly contacts between the study visits scheduled after Month 3 to collect safety information and to record the occurrence of HZ or to collect follow-up information regarding any HZ episodes.

For both studies, solicited symptoms were recorded by a subset of subjects on a diary card for 7 days following each vaccination. Local symptoms were injection site pain, swelling, and erythema, and general symptoms were fatigue, myalgia, shivering, headache, fever, and GI symptoms. All subjects recorded unsolicited adverse events for 30 days after vaccination on a diary card. Medically attended events were recorded from Month 0 to Month 8.

All serious adverse events, or SAEs, were recorded from Month 0 to Month 14, and related or fatal SAEs and potential immune-mediated inflammatory diseases, or pIMDs, were recorded throughout the study.

Non-ordinal solicited symptoms and unsolicited adverse

events were graded as Grade 1 mild, Grade 2 moderate, or Grade 3 severe, severe meaning preventing daily activity. Grade 3 swelling and erythema had a diameter of greater than 100 mm and fever, and Grade 3 fever, taken by the oral, axillary, or tympanic route, was greater than or equal to 37.5 degrees centigrade and greater than 39 degrees centigrade, respectively.

Clinically suspected cases of herpes zoster were assessed the same way in both studies. On the left of the slide, you can see the subjects with clinically suspected HZ had additional assessments, which included sampling of available rash lesions for VZV testing by polymerase chain reaction assay, photographic documentation of the rash, and assessment of HZ-related pain which was recorded until a 4-week pain-free interval was achieved.

Additionally, HZ-related complications, including postherpetic neuralgia or PHN, and HZ-related activities, such as physician visits and concomitant medications taken, were recorded.

On the right side of the slide, you can see that clinically suspected HZ cases were confirmed by polymerase chain reaction testing of lesion samples. If a case was unable to be confirmed or excluded by PCR, confirmation was by a Herpes Zoster Adjudication Committee, or HZAC, comprised of five physicians with herpes zoster expertise, which adjudicated

each clinically suspected case.

For the purposes of the study, a suspected case of HZ was defined as a new unilateral rash accompanied by pain and no alternative diagnosis. PHN was defined as the presence of HZ-associated severe worst pain persisting or appearing more than 90 days after the onset of the HZ rash. Severe worst herpes zoster-associated pain was pain rated as greater than or equal to 3 out of 10 on a scale included in the Zoster Brief Pain Inventory, a validated HZ-specific pain assessment questionnaire.

Studies Zoster-022 and -006 had a number of analysis populations. The populations most relevant to the discussion of safety and efficacy are the total vaccinated cohort and the modified total vaccinated cohort.

The total vaccinated cohort, or TVC, consisted of subjects who received at least one dose by product actually administered. This was the primary analysis population for safety assessment.

The modified total vaccinated cohort, or mTVC, consisted of subjects who received both doses and did not have an episode of HZ prior to 1 month after Dose 2. This was the primary analysis population for efficacy.

Let's first discuss Zoster-006. Subjects 50 years of age and older were eligible for the study. The study population was stratified 8:5:3:1 for the following age strata: 50 to 59,

60 to 69, 70 to 79, and greater than or equal to 80 years of age. Approximately 58% of subjects participated in the 7-day diary card subset for the collection of solicited symptoms, and all subjects greater than or equal to 70 years of age were included in this subset.

The success criterion for the primary endpoint of Zoster-006 would be met if the lower bound of the two-sided 95% confidence interval for herpes zoster vaccine efficacy in subjects greater than or equal to 50 years of age was above 25%.

The triggers for the final herpes zoster efficacy analysis were event driven with a pre-specified minimum follow-up period, and these conditions were reached prior to the triggers for the end-of-study analyses. The end-of-study analyses, conducted at the same time as the analyses of Zoster-022, evaluated most of the secondary efficacy endpoints and all of the safety endpoints.

The demographic profile of the subjects in the TVC at the end of the study was comparable between treatment groups. The mean and median ages were 62 and 60 years of age, respectively, and the proportions of females higher than males. The majority of subjects were white of European heritage and were not of Hispanic or Latino ethnicity. At least one pre-existing medical condition was reported by the majority of subjects, and the proportions of subjects reporting medical conditions were

comparable between the treatment groups. There were no clinically relevant differences between the treatment groups for the proportions of subjects reporting conditions by preferred term or system organ class. The demographic profile of the population evaluated for efficacy, the mTVC, was comparable to the TVC.

Here are the proportions of subjects by region for TVC at the end of the study. This is similar to the proportions at the mTVC at the final HZ efficacy analysis. As you can see, the majority of subjects were from Europe.

At the end-of-study analysis, the total enrolled cohort included 8,068 subjects in the Shingrix and 8,078 subjects in the placebo group. As can be seen from the bottom row, 95.4% of enrolled subjects in each treatment group were included in the TVC, the primary population for safety analysis; 91% of the excluded subjects were from a single site in Mexico. Data from this site could not be endorsed by the Applicant due to serious deviations from good clinical practice, or GCP. These subjects were analyzed for safety separately.

The number and proportions of subjects in the TVC excluded from the mTVC is presented here. At the final herpes zoster efficacy analysis, from the bottom row, 95.4 and 96.1% of subjects in the TVCs of the Shingrix and placebo groups, respectively, were included in the mTVC for the final herpes zoster efficacy analysis. The primary reason that subjects in

the TVC were excluded from the mTVC was due to not receiving two doses; 4.4% and 3.6% of subjects in the Shingrix and placebo groups did not receive two doses.

This slide presents the proportions of subjects who did not receive a second dose with the reasons for withdrawal from vaccination specified by more than 2% of subjects in either group. The most common reason for not receiving a second dose was "Visit not done."

Note that although low compared to the study population overall, the proportions of subjects not receiving a second vaccination due to non-serious unsolicited AEs and non-serious solicited AEs were higher in the Shingrix than the placebo group.

Per protocol, a subject who completed the last study contact was considered to have completed the study; 88.2% of the subjects completed the study, and the proportions who completed and withdrew were comparable between vaccination groups.

This table presents the reasons for study withdrawal by vaccination group. The most common reasons for withdrawal were consent withdrawal not due to an adverse event, serious adverse event, and lost to follow-up in subjects with a complete vaccination course.

In general, the proportions of subjects in Zoster-006 who withdrew for various reasons were comparable between

vaccination groups. Although not presented here, the proportions of subjects who withdrew by age group increased with increasing age for both vaccination groups.

Now we will move on to the efficacy analysis in Zoster-006. This slide provides the number of subjects in the mTVC of each treatment group overall who contributed to the final herpes zoster efficacy analysis, large *N*, and the numbers of subjects who reported confirmed HZ, small *n*, during the time at risk (T years) for the calculation of herpes zoster vaccine efficacy.

After a median follow-up time of 3.1 years, there were six subjects with confirmed cases of HZ in the mTVC of the Shingrix group and 210 with confirmed HZ in the mTVC of the placebo group. The incidence of HZ in the Shingrix group was 0.3 per 1,000 person-years, and the incidence of HZ in the placebo group was 9.1 per 1,000 person-years. Calculated Shingrix herpes zoster vaccine efficacy was therefore 97.16% with a lower bound of the 95% confidence interval being 93.72%. The primary efficacy success criterion for Zoster-006 was met, as the lower bound of the 95% confidence interval for the point estimate of herpes zoster vaccine efficacy was above 25%.

The primary efficacy analysis of herpes zoster vaccine efficacy was supported by a sensitivity analysis by age strata. The Applicant's pre-specified criteria for meaningful herpes zoster vaccine efficacy in the 50 to 59 and 60 to 69 year-old

age strata were met, as the lower bound of the 95% confidence interval of herpes zoster vaccine efficacy for each stratum was above 10%.

There was no pre-specified success criterion for herpes zoster vaccine efficacy in the greater than or equal to 70 years of age stratum in the study, but as can be seen from the herpes zoster vaccine efficacy column on the right, herpes zoster vaccine efficacy was comparable between the age groups.

As previously discussed, clinically suspected herpes zoster cases were confirmed by PCR testing for VZV in lesion samples, or by an expert Herpes Zoster Adjudication Committee. Overall, at the final herpes zoster efficacy analysis, 89.4% of cases were confirmed by PCR, 66.7% in the Shingrix and 90.0% in the placebo group.

Due to power considerations, there were no pre-specified success criteria for the evaluation of herpes zoster vaccine efficacy by time, but as you can see from the vaccine efficacy column on the right, herpes zoster vaccine efficacy appears durable up to Year 4 post-vaccination.

Overall PHN vaccine efficacy was a secondary endpoint of Zoster-006. It was calculated similarly to the herpes zoster primary endpoint and considered all subjects in the mTVC, not just those with confirmed HZ.

At the end-of-study analysis, there were no subjects in the Shingrix group who reported PHN, and there were 18 subjects

who reported PHN in the placebo group, for an overall PHN vaccine efficacy of 100%.

An analysis of PHN vaccine efficacy in subjects with confirmed HZ across both studies was performed. It will be provided later in the presentation.

This slide presents, on the left, select secondary efficacy objectives, analyzed on subjects with confirmed HZ. The Applicant was unable to conclude on these secondary objectives, so no reliable conclusions can be drawn.

In terms of herpes zoster-related complications, no subjects reported more than one. Additionally, herpes zoster complications were not reported in the Shingrix group, and in the placebo group, there was one subject each reporting herpes zoster vasculitis and ophthalmic disease and four subjects reporting disseminated disease.

The next three slides summarize the frequencies of subjects reporting solicited symptoms following vaccination with both doses considered. These data were provided in more detail in the briefing document.

This slide presents the proportions of subjects in each treatment group who reported at least one solicited symptom with the proportions of subjects who reported Grade 3 solicited symptoms highlighted in red. From the first column on the left, the proportions of the subjects in the Shingrix group reporting at least one solicited symptom of any grade was

85.2%, with 16.4% reporting at least one Grade 3 symptom. From the next three columns, the proportions of subjects in the Shingrix group reporting at least one any grade and Grade 3 solicited symptom decreased with increasing age. Although not presented on the slide, the proportions of subjects in the Shingrix group reporting at least one any grade and Grade 3 solicited symptom were generally comparable between Dose 1 and Dose 2.

The proportions of subjects in each treatment group who reported at least one solicited local symptom and the proportions reporting each solicited local symptom are presented here. The proportion of subjects in the Shingrix group reporting at least one any grade local symptom was 81.5%, with 9.5% reporting at least one Grade 3 local symptom.

Pain was the most commonly reported local symptom. The proportions of subjects in the Shingrix group reporting at least one any grade or Grade 3 local symptom was generally comparable between Dose 1 and Dose 2. The median duration of pain, redness, or swelling in the Shingrix group was about 3 days.

This slide presents the proportions of subjects in each treatment group who reported at least one solicited general symptom and the proportions reporting each solicited general symptom. Looking at the column on the left, the proportion of subjects in the Shingrix group reporting at least one of any

grade general symptom was 66.1%, with 11.4% reporting at least one Grade 3 general symptom.

Fatigue and myalgia were the most commonly reported general symptoms in the Shingrix group. The proportions of subjects in the Shingrix group reporting most general symptoms increased marginally from Dose 1 and Dose 2 except for shivering; the proportions of subjects reporting Grade 3 shivering doubled from 1.6 following Dose 1 to 3.3% following Dose 2. The median duration of the general symptoms in the Shingrix group was 1 to 2 days.

Here we have the proportions of subjects reporting SAEs during select time periods post-vaccination. Generally, these proportions were balanced overall and by system organ class and preferred term between treatment groups. However, CBER noted a small difference between treatment groups in the proportions of subjects reporting cardiac arrhythmias and supraventricular tachyarrhythmias, as seen on the next slide.

CBER utilized standardized MedDRA queries, or SMQs, for safety signal analyses. SMQs are validated, pre-determined sets of MedDRA terms used to facilitate the retrieval of MedDRA coded data as a step in investigating safety issues.

Using SMQs, CBER detected a difference between treatment groups for the proportions of subjects reporting events captured in the narrow cardiac arrhythmias superordinate SMQ and the supraventricular tachyarrhythmias sub-SMQ during

different time periods. The differences appear to be driven, in part, by imbalances between treatment groups for the proportions of subjects reporting for the preferred terms of atrial fibrillation and palpitations and to a lesser extent supraventricular tachycardia.

Of note, there did not appear to be an imbalance between treatment groups for the SMQ of ventricular tachyarrhythmias in Zoster-006, and no difference between treatment groups for these cardiac arrhythmia SMQs was noted for Zoster-022 or for the pooled analysis.

Potential immune-mediated inflammatory diseases were recorded throughout the study. Comparative analysis indicated that there was no difference between vaccination groups for the proportions of subjects reporting pIMDs overall or by SOC or PT during Month 0 to Month 14. Additionally, no clinically significant imbalances were noted between treatment groups with regard to the incidence of the most commonly reported pIMDs during the select time periods in which they were tabulated.

The proportions of subjects who died during select time periods post-vaccination were similar between vaccination groups. There were no clinically significant imbalances noted between treatment groups for the proportions of subjects who died when analyzed overall or by specific preferred term or system organ class for the select time periods.

Now, moving on to Zoster-022, the following are design and

analysis specifics for that study. Subjects 70 years of age and older were eligible. The study population was stratified 3:1 for the age strata 70 to 79 and greater than or equal to 80 years of age. Approximately 7% of the subjects were randomized into the 7-day diary card subset for the collection of solicited symptoms.

The success criterion for the study would be met if the lower bound of the two-sided 95% confidence interval of herpes zoster vaccine efficacy in subjects greater than or equal to 70 years of age was above 10%.

Demographic profile of the subjects in the TVC at the end of study was comparable between vaccination groups. The mean and median ages were 76 and 74 years, respectively, and the proportions of females was slightly higher than males. Again, the majority of subjects were white of European heritage and were not of Hispanic or Latino ethnicity. The demographic profile of the population evaluated for efficacy, the mTVC, was comparable to the TVC.

At least one pre-existing medical condition was reported by the majority of subjects, and the proportions of subjects reporting medical conditions were comparable between treatment groups. There were no relevant differences between the groups for the proportions of subjects reporting conditions by preferred term or system organ class.

This table presents the distribution of subjects by

region. Similar to Zoster-006, the majority of subjects were from Europe.

The total enrolled cohort included 7,408 subjects in the Shingrix and 7,406 subjects in the placebo group. As can be seen from the bottom row, 93.8% of enrolled subjects in each treatment group were included in the TVC, and similar to Zoster-006, 94.6% of those excluded were from the site in Mexico which had deviations from GCP. These subjects were analyzed for safety separately.

94.3% and 95.2% of subjects in the TVC of the Shingrix and placebo groups, respectively, were included in the mTVC for the herpes zoster efficacy analysis in Zoster-022. Again, the primary reason that subjects in the TVC were excluded from the mTVC was due to not receiving two doses; 5.6 and 4.4% of the Shingrix and placebo groups, respectively, didn't receive two doses.

This slide presents the numbers of subjects who did not receive a second dose and the reasons for withdrawal from vaccination specified for more than 2% of the subjects in either group. Again, the most common reason for not receiving the second dose is in the bottom row, and it is "Visit not done."

A subject who completed the last study contact was considered to have completed the study. Of subjects in the TVC, 82.9% completed the study, and the proportions who

completed and withdrew were comparable between vaccination groups.

The reasons for study withdrawal by vaccination group for subjects in the TVC are presented here. The most common reasons for withdrawal were serious adverse event and consent withdrawal not due to an adverse event. In general, the proportions of subjects who withdrew in Zoster-022 for various reasons were comparable between vaccination groups.

This slide presents the numbers for analysis of the primary herpes zoster efficacy endpoint. After a median follow-up time of 3.9 years, there were 23 confirmed cases of HZ in the mTVC of the Shingrix group and 223 in the mTVC of the placebo group. The incidence of HZ in the Shingrix group was 0.9 per 1,000 person-years, and the incidence of HZ in the placebo group was 9.2 per 1,000 person-years.

Calculated Shingrix herpes zoster vaccine efficacy was 89.79% with a lower bound of the 95% confidence interval being 84.29%. The primary study objective of Zoster-022 was therefore met as the lower bound of the 95% confidence interval for the point estimate of herpes zoster vaccine efficacy was above 10%.

Although Zoster-022 was not designed to demonstrate herpes zoster vaccine efficacy for each age stratum, as can be seen from the column on the right, the estimates of herpes zoster vaccine efficacy were comparable for the two age strata.

Here we can see that 92.3% of cases in Zoster-022 were confirmed by PCR, 82.6% in the Shingrix and 93.3% in the placebo group.

Again, due to power considerations, there were no pre-specified success criteria for the evaluation of herpes zoster vaccine efficacy by time. However, from the column on the right of this slide, vaccine efficacy appears durable to Year 4 post-vaccination.

This table contains the analysis of overall PHN vaccine efficacy on the mTVC. Recall that the overall PHN vaccine efficacy endpoint was calculated the same way as the herpes zoster vaccine efficacy endpoint. From the table above, small *n*, there were four subjects in the Shingrix group and 28 in the placebo group reporting PHN, for an overall PHN vaccine efficacy of 85.49%.

This slide on the left presents the secondary efficacy objectives that were analyzed on subjects with confirmed HZ. The Applicant was unable to conclude on the first two objectives. The Applicant concluded on the objective regarding the use of pain medications by subjects with confirmed HZ in the Shingrix as compared to the placebo group, with a vaccine efficacy of 39.6% and a lower bound of the 95% confidence interval of 10.79%.

Regarding herpes zoster complications, one subject in the Shingrix group, or 4.3% of subjects with confirmed HZ, reported

a complication of ophthalmic HZ, and 10 out of 223, or 4.5% of subjects with confirmed HZ in the placebo group, reported herpes zoster complications of disseminated disease, ophthalmic disease, and neurologic disease.

The next three slides will briefly summarize frequencies of solicited symptoms following vaccination with both doses considered.

The proportions of subjects in the Shingrix group reporting at least one solicited symptom of any grade was 79%, with 11.9% reporting at least one Grade 3 solicited symptom. In the Shingrix group, the proportions of subjects reporting at least one solicited symptom of any grade decreased slightly with increasing age while the proportions reporting at least one Grade 3 solicited symptom were similar between the age strata.

Although not presented on the slide, the proportions of subjects in the Shingrix group reporting at least one solicited symptom and one Grade 3 solicited symptom were generally comparable after Dose 1 and Dose 2.

This slide presents the proportions of subjects in each treatment group who reported at least one solicited local symptom and each solicited local symptom.

The proportion of subjects in the Shingrix group reporting at least one local symptom of any grade was 74.1% with 8.5% reporting at least one Grade 3 local symptom. Pain was the

most commonly reported local symptom, and the proportions of subjects in the Shingrix group reporting any grade or Grade 3 local symptom was generally comparable between Dose 1 and Dose 2. The median duration of local symptoms in the Shingrix group was 2 to 3 days.

This slide presents the proportions of subjects in each treatment group who reported at least one solicited general symptom and each general symptom.

The proportion of subjects in the Shingrix group reporting at least one general symptom of any grade was 53% with 6% reporting at least one Grade 3 general symptom. Fatigue and myalgia were the most commonly reported general symptoms in the Shingrix group. The proportions of subjects in the Shingrix group reporting any grade and Grade 3 of each general symptom marginally increased after Dose 2 as compared to Dose 1, except for any grade and Grade 3 shivering. The proportions of subjects reporting any grade and Grade 3 shivering increased from 7.6% to 12% and 0.2% to 1%. The median duration of general symptoms in the Shingrix group was 1 to 2 days.

Presented here are the proportions of subjects in the TVC of each vaccination group who reported an SAE during time periods relative to vaccination in Zoster-022. The proportions were comparable between vaccination groups, and there were no clinically significant differences in the proportions of subjects reporting events by SOC or PT during these periods.

The proportions of subjects reporting pIMDs in Zoster-022 during select time periods is also presented. No clinically significant imbalances were noted between treatment groups with regard to the incidence of the most commonly reported pIMDs during the select time periods in which they were tabulated.

The proportions of subjects who died during select time periods post-vaccination in Zoster-022 is presented here. Again, there were no clinically significant imbalances noted between treatment groups for the proportions of subjects who died when analyzed overall or by specific preferred term or system organ class for the select time periods.

Now we're going to discuss the results, the pooled results, from the pivotal studies. There were two pooled safety analyses: the main pooling, consisting of subjects in Zoster-006 and Zoster-022, and the broader pooling analysis which included an additional 848 subjects from several other Phase II and III studies who received at least one dose of Shingrix on a Month 0, Month 2 schedule and who had at least 1 year of safety follow-up post-vaccination prior to the data lock point for safety analyses. Only SAEs, pIMDs, and deaths were analyzed on this broader pooling.

As no safety signals were noted for the additional 848 subjects in the broader pooling, only the safety results from the main pooling will be discussed in this presentation.

This slide presents the proportions of subjects who

reported at least one SAE during select time periods post-vaccination, which were comparable between vaccination groups. In general, the proportions of subjects reporting events by SOC and PT were also comparable, except for the preferred term of supraventricular tachycardia, which was reported by higher proportions in the Shingrix group during the 365-day post-vaccination period, six reports versus zero reports. No difference between treatment groups, however, was noted by CBER for events reported in the supraventricular tachyarrhythmias SMQ for the pooled analysis for this period.

Here are some of the most commonly reported preferred terms for SAEs tabulated for the 365-day post-vaccination period. The proportions of subjects reporting these specific events by preferred term were generally similar between vaccination groups. You'll notice, however, that more subjects in the Shingrix group reported the specific preferred terms of pneumonia and cerebrovascular accident in this analysis, so CBER performed additional analyses of these events, presented in the next slide.

Using SMQs, CBER queried the database for medically attended events from Months 0 to Month 8, a little closer to vaccination, in the central nervous system vascular disorders SMQs and sub-SMQs, and the proportions of subjects reporting these events appeared comparable between vaccination groups.

Additionally, while there is no standardized MedDRA query

for the general term of pneumonia, CBER analyzed the proportions of subjects reporting events under the higher-level term of lower respiratory tract and lung infections, which contains the preferred term of pneumonia, and observed no imbalance between treatment groups for these events.

Fifteen subjects in each treatment group had SAEs, listed above, that were judged related to vaccination by the investigators. No SAEs were judged related to Shingrix vaccination by the Applicant. CBER considers that two of these SAEs were likely related to Shingrix due to biologic plausibility, temporal relationship to vaccination, and lack of plausible alternative etiologies.

These are bolded. One subject reported lymphadenitis temporally associated with both vaccinations which led to surgical intervention to rule out a malignant process, and the other subject reported injection site events, chills and pyrexia greater than 39 degrees centigrade the day after vaccination.

Although causal relationship to study vaccination could not be ruled out for the other events in the Shingrix group, CBER could not ascribe a causal relationship due to one or more factors such as information suggesting an association with the vaccine procedure instead of the vaccine itself, information suggesting other potential alternative etiologies, a lack of temporal association, lack of clustering of similar events

temporally associated with vaccination, lack of biologic plausibility, and/or no difference between the Shingrix and placebo groups for the occurrence of the event.

One death was judged vaccine related by the investigator but not the Applicant; this event is starred in the Shingrix group on the left. The subject was greater than 90 years of age with a past medical history of stable immune thrombocytopenia for 10 years who was noted to be pancytopenic 72 days after Dose 1. He was diagnosed with acute myeloid leukemia 3 days after the pancytopenia diagnosis and developed neutropenic sepsis 97 days after Dose 1, dying 1 day later.

This slide presents the proportions of subjects in each treatment group who reported at least one pIMD during select time periods post-vaccination in the pooled analysis. No clinically significant differences were noted between treatment groups for the proportions of subjects reporting events overall or by specific preferred term or SOC.

Serious pIMDs judged related to vaccination by the investigator were presented in that earlier slide. This slide presents the non-serious pIMDs judged related to vaccination by the investigator. No pIMDs were judged related to Shingrix vaccination by the Applicant. CBER reviewed these narratives, and although a causal relationship to Shingrix could not be ruled out, causality for events in the Shingrix group could not be ascribed to Shingrix due to alternative etiologies, lack of

temporal association, and/or lack of clustering of similar events associated with Shingrix vaccination.

This slide presents the proportions of subjects in each treatment group of the main pooling who died during time periods relative to vaccination. No clinically significant imbalances were noted when analyzed by overall deaths or by specific SOC or PT.

The proportions of subjects reporting unsolicited AEs during the 30-day post-vaccination period were not presented separately for Zoster-006 and Zoster-022 but are presented here for the pooled analysis.

On the left are unsolicited adverse events reported by higher frequencies of subjects in the Shingrix group that were not included as specific solicited events on the 7-day diary card and were reported by more than 1% of subjects in the Shingrix group. These are as follows: injection site pruritis, malaise, pain, injection site warmth, dizziness, upper respiratory infection, arthralgia, nausea, and pain in extremity.

The events on the right were also reported by higher frequencies of subjects in the Shingrix group. They were reported by less than 1% but at least 30 subjects in the Shingrix group and were as follows: influenza-like illness, asthenia, feeling hot, feeling cold, respiratory tract infection, decreased appetite, somnolence, lethargy, insomnia,

hyperhidrosis, and gout.

The events included on this slide are vaccine-associated events of interest.

Anaphylaxis: One subject in the Shingrix group reported an event coded by preferred term as Grade 1 anaphylaxis temporally associated with vaccination. From the dataset, this subject reported Grade 1 injection site pain and erythema and Grade 3 pyrexia, fatigue, nausea, chills, and disorientation on Day 0 after Dose 1. The events resolved by Day 3 without medical attention, and the Applicant and CBER assessed the case according to the Brighton case definition as not a case of anaphylaxis.

Guillain-Barré syndrome: Two subjects reported GBS during the year post-vaccination, one in the Shingrix group 181 days after Dose 2, and one in the placebo group 39 days after Dose 2.

The select events on this slide and the next slide do not imply causality but were included because of imbalances noted between treatment groups with more subjects in the Shingrix as compared to the placebo group reporting. These events in this slide will be addressed in the pharmacovigilance plan.

Osteonecrosis: Five subjects in the Shingrix group reported six events of the specific preferred term of osteonecrosis in the year post-vaccination; none were reported during that period in the placebo group. The events were

recorded 4 days after Dose 1, and 75, 95, 132, and 178 days after Dose 2. Three events in two subjects were coded as exacerbations. Narratives suggest that the other subjects reported some worsening of pain prior to vaccination.

Gout and gouty arthritis: During the 30-day post-vaccination period, 27 and 8 subjects in the Shingrix and placebo groups, respectively, reported gout or gouty arthritis. Of these subjects, 19 in the Shingrix group and 3 in the placebo group reported gout for the first time during this period.

Arthralgia: An imbalance was noted in the proportions of subjects reporting arthralgia during the 30-day post-vaccination period; 1.72 and 1.17% of subjects reported arthralgia in the Shingrix and placebo groups, respectively, during this period.

Optic ischemic neuropathy, or OIN: Three subjects reported OIN within 50 days post-vaccination in the Shingrix group. No OIN was reported in the placebo group. Two events were serious, and both subjects with these SAEs had negative temporal artery biopsies.

Arteritic OIN is associated with temporal arteritis and is inflammatory in nature, and the more common non-arteritic type is associated with ischemia or small vessel circulatory insufficiency. Arteritic and non-arteritic OIN have been reported at rates of 0.4 to 1.3 and 2.3 to 10.2 per 100,000

person-years, respectively.

In light of the imbalance in subjects reporting OIN, CBER looked in the datasets for other ocular events and did not find any clinically significant differences between treatment groups with regard to other ocular inflammatory, ocular vascular, or ocular neurovascular events associated with vaccination.

Convulsions: CBER analysis noted an imbalance in the number of subjects (eight in the Shingrix and one in the placebo group) reporting events by preferred term contained in the narrow standardized MedDRA query of convulsions during the 30-day post-vaccination period. Available data were reviewed, and two subjects had alternative etiologies for their convulsions, and another two had a prior history of convulsions. It is noted that some events were non-serious, and as such, no narratives could be reviewed.

Supraventricular tachyarrhythmias: As reported previously, there was an imbalance in the proportions of subjects reporting events in the narrow supraventricular tachyarrhythmias SMQ for Zoster-006, but this imbalance was not observed in Zoster-022 or the main pooling.

Amyotrophic lateral sclerosis, or ALS: Three subjects in the Shingrix group reported ALS at 80, 173, and 211 days post-Dose 2 in the Shingrix group, and one reported ALS in the placebo group, possibly in the year post-vaccination, which was not included as an SAE but was in the narrative of death. The

incidence of ALS is approximately 2 per 100,000 person-years.

We're going to move on to the efficacy analysis for the pooled studies now. The co-primary objectives for the pooled analysis of Zoster-006 and 022 re-estimated herpes zoster vaccine efficacy and evaluated overall PHN vaccine efficacy in subjects greater than or equal to 70 years of age. Note the pre-specified success criterion for the PHN vaccine efficacy objective.

A secondary objective evaluated PHN vaccine efficacy across both studies in subjects with confirmed HZ, greater than or equal to 50 years of age with confirmed HZ.

This slide provides the re-estimation of herpes zoster vaccine efficacy across both studies for subjects greater than or equal to 70 years of age. In this analysis, the herpes zoster vaccine efficacy point estimate was 91.3%, and this was concordant with that from Zoster-022, which was 89.79%.

The other co-primary objective was to evaluate vaccine efficacy against overall PHN across both studies in subjects greater than or equal to 70 years of age. As the lower bound of overall PHN vaccine efficacy was greater than 0 at 88.78%, the success criterion for the overall PHN vaccine efficacy endpoint for the pooled analysis was met.

This slide presents PHN vaccine efficacy in subjects with confirmed HZ across both studies. In subjects greater than or equal to 50 years of age with confirmed HZ in the mTVC, there

were 4 subjects out of 32, or 12.5%, who reported PHN in the Shingrix group and 46 subjects out of 477, or 9.64%, who reported PHN in the placebo group. Vaccine efficacy in terms of reduction in PHN incidence in subjects with confirmed HZ was 0.29% with a lower bound of the 95% confidence interval below zero.

Now, to summarize CBER's review, CBER's efficacy conclusions are as follows: The clinical endpoint studies confirmed Shingrix herpes zoster vaccine efficacy. Herpes zoster vaccine efficacy appears durable to Year 4. Prevention of PHN by Shingrix appears to be attributable to the prevention of HZ.

CBER's safety conclusions are as follows: Local and general reactogenicity and Grade 3 reactogenicity were commonly reported after Shingrix vaccination. While common in all age groups, reactogenicity was higher in younger as compared to older subjects. Overall, SAEs, deaths, and pIMDs were reported in similar proportions of subjects during time periods post-vaccination. And continued pharmacovigilance is planned to further inform the safety profile of Shingrix.

That's it.

DR. EDWARDS: Thank you very much.

Are there questions?

DR. JANES: Okay, thank you. So an aspect of these efficacy trial designs that hasn't come up in the previous

questions is the observer blinding versus double blinding of the -- that I understand was used.

So, you know, to what extent has -- have you or GSK considered that issue and the extent to which it might have affected the reporting of zoster events, or perhaps more importantly, the more subjective safety events or rating of safety severity events?

In my mind, it seems to unnecessarily complicate the interpretation of the results, although I suspect that any bias that would've been introduced would certainly not have been large enough to explain the high levels of efficacy that were seen.

DR. AGGER: One of the things that you might have noticed was that equal proportions of SAEs were reported, as related, by the investigator. So that gave us some confidence that, you know, they were truly kind of considering, you know, even if someone had a Grade 3 event, it didn't necessarily mean that they were in the Shingrix group even though higher proportions had that. But I don't know if GSK would like to respond to that. We felt a little bit more comfortable seeing that equal proportions were judged related.

DR. MILLER: Yes. So as Dr. Agger stated, we believe that if there was any bias in the safety analysis, it would've been in the HZ/su group. I'd like to invite Dr. Oostvogels, who is responsible for the trial, to comment on the rationale for

blinding in the way that we did.

DR. OOSTVOGELS: Lidia Oostvogels from the clinical team.

So, in effect, we were obliged to use an observer blinding design, blind design, because actually the -- we were not able to make a placebo that was from aspect exactly the same, so the people that administered the vaccine were afterwards not implicated in the assessment of any of the endpoints or collection of the data. So that is actually the reason why we could not do a double-blind design, which, of course, is always ideal.

DR. EDWARDS: Other questions? Yes.

MR. TOUBMAN: It was asked in the morning about the very low rate of African or African-American participation. It was, I believe, 1.1% and 1.8%. And I just wanted to know, is that unusual, or is that something you tend to see in these studies?

DR. AGGER: I think we generally see, you know, white of European heritage being the most common group pretty commonly in these vaccine clinical trials. I don't think that's unusual, although we do encourage sponsors to, you know, broaden the diversity of their pool. You know, it's sometimes not possible to do that.

DR. EDWARDS: Could you comment on those individuals who had had zoster before and then were vaccinated? Did it appear that their adverse reaction profiles were comparable to those that had never had zoster?

DR. AGGER: I would have to defer to the Applicant on that. That's Zoster-033 you're talking about. I would have to defer to the Applicant on that one.

DR. MILLER: So, Dr. Edwards, can I ask you to repeat your question just to make sure I understood it correctly?

DR. EDWARDS: So in those individuals who had had clinical herpes zoster before who were vaccinated, were their reaction profiles comparable to those who had never had herpes zoster before?

DR. MILLER: Yeah. So the reactogenicity profile was actually comparable to the general population that we saw in the Phase III study.

DR. EDWARDS: Thank you.

DR. MILLER: Thank you.

DR. AGGER: I thought it was, but I wasn't sure, so I didn't want to misspeak.

DR. EDWARDS: Are there any other -- yes, Dr. Kotloff.

DR. KOTLOFF: So I wanted to come back again to the supraventricular tachycardias and gout, in particular. Will there be any special precautions because of the possible association and any particular monitoring that will be advised as a result of these possible associations?

DR. AGGER: I believe it's included in the pharmacovigilance plan proposed by the Sponsor. I'd also like to remind you that the differences that we saw in the

supraventricular tachyarrhythmias was only in Zoster-006. If you can bring up backup slide -- let's see. Number 14. No, backup slide. Backup slide.

(Pause.)

DR. AGGER: Oh, it's nice.

UNIDENTIFIED SPEAKER: All right.

DR. AGGER: Uh-huh. Oh, that's nice.

(Pause.)

DR. AGGER: Okay, so here are the proportion of subjects in 006 and 022 reporting events by preferred term in the cardiac arrhythmia SMQs, reporting some of the events by preferred term. And you can see, in the first two columns there were reports of atrial fibrillation in the Shingrix group as compared to the placebo group in Zoster-006, but the opposite is true for Zoster-022. The reports where palpitations varied and the reports of SVT were few but were higher in the Shingrix as compared to the placebo group during the various time periods.

So does the Applicant want to discuss their plans for monitoring supraventricular tachycardia?

DR. STEGMANN: Jens Stegmann, Clinical Safety/Pharmacovigilance, GSK.

Because of the interest for that kind of area and events and -- and also the numerical, the numerical imbalance noted, we plan to make this concept part of the pharmacovigilance

plan, which is going -- which you see here. So this applies for the element of this standard pharmacovigilance which is based on continuous report and clinical and nonclinical information, as well for the targeted safety study, which is following up medically attended adverse events of interest to further evaluate and inform about the safety profile we're having on that. So this concept is addressed.

DR. KOTLOFF: The gout and whether this has -- in the people who had new onset gout, was this just an isolated episode and then it went away, or is there an ongoing risk, and how will you --

DR. STEGMANN: The majority of the patients who reported gout in the clinical study had either already gout being reported previously or respective risk factors for that. And with the gout and gouty arthritis, it's going to be addressed, in addition to what I just described, in the classical pharmacovigilance and targeted safety study, also in the enhanced pharmacovigilance plan that we would -- specific targeted follow-up procedures, enabling us just to see whether the reported cases do exceed what's been expected. So this is being addressed in all three parts of the proposed pharmacovigilance plan.

DR. KOTLOFF: And just to clarify, because I've heard two ways that there was an imbalance in new onset gout --

DR. STEGMANN: Um-hum.

DR. KOTLOFF: -- but the majority had previous gout, so I'm a little bit confused which is the case.

DR. STEGMANN: The new onset gout, these are subjects who have reported risk factors, might not be documented as gout episodes by enrollment of that, but have reported risk factors which do lead to gout later on, and these were captured in the analysis I've shown to you as new onset of gout.

DR. EDWARDS: Dr. Englund.

DR. ENGLUND: I just wanted to thank the FDA for their pooling with the SMQ, which for those who have been on this Committee, the standardized reference to the CNS orders and the LRTI disorders, that helps explain it to me, so thank you for presenting that data because that helps me understand. So thank you.

DR. AGGER: You're welcome.

DR. EDWARDS: Dr. Long.

DR. LONG: Was CBER able to look at the relationship of the country of the subjects in both their pre-immunization antibody levels and their response and the efficacy?

It still is somewhat bothersome to consider licensure for a product for United States adults with relatively little information on United States adults, and the differences in epidemiology of the disease varicella in countries, where we haven't had very much varicella in the last 20 years in the United States, and these 50-year-olds wouldn't have had much

boosting, whereas that's not the case in many of the other countries in which the vaccine was studied.

So I'm wondering both a little bit on Dr. Sawyer's question, would you need two doses in some countries and one dose in other countries, and how do we know if a person has received zoster vaccine in the past, if that person might need one or two?

DR. AGGER: I don't know if I can answer that last question, because the clinical studies weren't designed to evaluate one dose. But we do have some information on vaccine efficacy by gender and region, if that would help. The region for North America, of course, includes --

DR. LONG: Canada.

DR. AGGER: -- United States and Canada, which was also included in the studies. Can you pull up Slide 10, please, from the backup?

Okay. So here we have Zoster-006, herpes zoster vaccine analysis by gender and region. You can see that North America is on the bottom of this one, and then for the next slide, we have it for 022. There it is again on the bottom. So vaccine efficacy is comparable.

DR. LONG: Thank you.

DR. AGGER: I can't really recall the specific baseline humoral responses for each region right now, so I can't really speak to that. There were some differences in the occurrence

of herpes zoster in the placebo group by region, so I surmise that there might've been some differences in humoral immunogenicity, but I just can't speak to that right now. Do you --

DR. MILLER: So maybe to answer your question, Dr. Long, which I think really has to do with could there be differences based on differences in our vaccination patterns around the world, we did enroll in 18 different countries. And as a way to look at this, we looked at our pre-vaccination antibody concentrations in the various countries where we enrolled, and we roughly put the countries into three different categories, so let me talk you through this particular slide.

But there are countries in the bar graphs, in peach, which are either low coverage or they have a very immature universal mass vaccination program. Countries in blue, which include the U.S. and Canada, so you see them all the way to the right in the bar graph, received two doses, and there's pretty high coverage of vaccine, 63 to 90%. And then the two countries in green, Australia and Taiwan, have a high coverage of one dose.

And with some regional differences, but largely overlapping 95% confidence intervals, even with the vaccination programs in place for a reasonably long time, 20 years in the case of the United States, we didn't really see differences between the countries.

DR. EDWARDS: Dr. Sawyer.

DR. SAWYER: Well, as long as we're talking about second doses, and this may be outside of what we're supposed to consider today, but in the FDA summary of Zoster-026 and in our background documents, it looks like individuals who received the second dose 12 months after the first dose had a lowered response, and that will have significant practical implications in rolling out a recommendation to administer this vaccine. So could somebody clarify just to what extent that looks like a concern?

DR. MILLER: So you were speaking about the Zoster-026 study, and while they pull up the slides, I'll just, because we didn't talk about it during the presentation, refresh everyone's memory.

It was a study where we used, as the control group, the 0, 2-month schedule. This is the group that has been bridged to efficacy, and we looked at a 0, 6-month schedule compared to 0, 2-month and then a 0, 12-month. Each of those schedules had two primary immunogenicity hypotheses. Both were matched for the 0, 6-month schedule; only one was met for the 0, 12-month schedule.

So the first hypothesis for both schedules, as we pull up the slide, was really based on demonstrating that the vaccine response rate, and this was a fourfold rise or greater in antibody titer from pre- to post-vaccination, was comparable, that percentage of subjects was comparable to what was seen in

the Phase III program, and this was the case, actually, for both the 0, 6-month, 0, 12-month schedule. So about 95% vaccine response rates were observed in the Phase III studies, and you see that that was comparable for both of the other two schedules. The statistical criterion that was set was a lower limit of the 95% confidence interval of 60%, and that was exceeded.

The second immunogenicity criterion that was utilized for both studies was a GMC ratio with the 0, 2-month schedule. And so that GMC ratio had a statistical criterion associated with an upper limit that had to be less than 1.5. So what you see for the 0, 6-month schedule is that the upper limit was 1.39, so that confidence interval was met. And then for the 0, 12-month schedule, it was marginally exceeded, and therefore, non-inferiority could not be declared for the 0, 12-month schedule.

DR. EDWARDS: Dr. Janes.

DR. JANES: So on that point, can you help us understand the extent to which those immune responses are predictive of efficacy? I've heard statements in both directions that there's fairly good evidence of surrogates of protection and, on the other hand, that there's not.

DR. MILLER: So I think, currently, no correlative protection exists for zoster reactivation, and it is true that it was an exploratory endpoint in our study to look for

correlative protection in terms of humoral immunity. That was a complex analysis that was not ready at the time that we submitted the BLA, and therefore, the FDA has not had the opportunity to review those responses.

But I think one thing that was maybe mentioned earlier and that may bear repeating is that we believe that both cellular and humoral immunity are important in terms of controlling infection. What's known is that both can contribute to cell killing, and the generalizability and stability of that assay and our ability to measure ELISA responses in the individuals across all countries was really the reason why we had picked that assay for our immunogenicity trials.

DR. EDWARDS: Yes, go ahead, Mr. Toubman.

MR. TOUBMAN: Back to GSK's CS-16, which is the time to onset pattern for cerebrovascular accident, I'm not certainly a statistician either, but it does seem, looking at this picture, that there's a lot of instances in the first 90 days; it just looks that way. So I guess my question is -- and if it was already answered, I apologize, but is looking at that going to be part of the pharmacovigilance plan that GSK is proposing?

DR. STEGMANN: Jens Stegmann, Clinical Safety and Pharmacovigilance.

What I would like to show you again is the analysis we have done for the 30 time period, the 30 days time period after vaccination and the 365 days time period of major

cerebrovascular events, which illustrates that for both categories, this is hemorrhagic cerebrovascular event and ischemic cerebrovascular event, there is no difference.

However, as we are speaking about an aging population where these kind of events do often occur, this is going to be addressed in the pharmacovigilance plan as well as we are looking into specifically for the targeted safety study as part of the integral part of the pharmacovigilance plan, also medically attended adverse events, which would enable us to just follow up specific those events or the number of events being reported in the postmarketing setting.

DR. EDWARDS: Dr. Sawyer.

DR. SAWYER: I have one more question about the generalizability of the results across racial and ethnic groups. I think you mentioned earlier that only three sites were able to do the cell-mediated immune response. Where were those sites, either geographically or can you characterize those populations compared to the overall?

DR. MILLER: So the countries where those CMI analyses were performed, there was one U.S. site, one site in the Czech Republic, and one site in Japan.

DR. SAWYER: So I'm going to guess that they maybe had even a lower percentage of Hispanic populations, for sure, if not African American, than your overall; is that correct?

DR. MILLER: I don't have the specific numbers

specifically at hand, but certainly in the Japanese population, for example, they were overwhelmingly Asian, and in Czech Republic also, mostly European, and most likely at the U.S. site, mostly Caucasian as well.

DR. EDWARDS: Dr. Kotloff.

DR. KOTLOFF: I apologize if you said this and I missed it, but for some of the key adverse events that were observed with possible imbalance, was there any difference between Dose 1 and Dose 2? Because it seems like mostly what we're looking at when it says less than 30 days, that could be within 30 days of either dose, but sometimes reactogenicity is seen in association with one dose more than another. So I'm wondering if there were any differential effects with any of these adverse events of interest.

DR. AGGER: The way I looked at them was I just kind of collated them and looked at them from time to onset from the dose. I didn't look at Dose 1 and Dose 2. For example, for optic ischemic neuropathy, there were only three events. For convulsions, I looked after 30 days after any dose.

So I don't remember how I looked at gout, if there were more after Dose 2 or Dose 1. Perhaps the Applicant can comment on that? I only looked within the 30-day post-vaccination period, after each dose. So I don't know whether there were more after Dose 1 or Dose 2. Do you recall? No, I don't have that on my number, sorry.

DR. EDWARDS: Dr. El Sahly.

DR. EL SAHLY: In the documents we received a week ago to review in advance of the meeting, there was a mention of a clinical trial where individuals received the HZ/su and they all had to have had zoster at one point before. And in the description of the data from that trial, there was mention of an increased risk of zoster in -- I mean, the way I calculated it, it ended up being 6 events in 90 individuals over a year, but we didn't get any debriefing on it today and there wasn't much more in the papers we received, so I wonder if having had zoster is something, a precaution or something we need to be concerned about.

DR. AGGER: Can you pull up backup Slide Number 3, please? So you're speaking about Zoster-033. It was a non-IND study conducted in two different countries. There were 96 subjects. It was a one-armed study, and there were 96 subjects who received two doses. There were six subjects, two of whom had more than one episode of prior HZ, who reported nine events of herpes zoster following vaccination during the 14 months; five of them received antiviral medication.

Of the subjects, those who received two doses were vaccine responders, so not clear why they would've experienced herpes zoster. An informal analysis by our statistician calculated the incidence at approximately 50 per 1,000 person-years, which is higher than you would expect from unvaccinated people, not

after vaccination. You know, the data were somewhat confusing, and the Sponsor has committed to performing a randomized controlled study in this population to get more and more robust information, and perhaps they'd like to speak about the plans for that study.

DR. MILLER: Yeah, so Jacqueline Miller, Clinical R&D, GSK.

As Dr. Agger mentioned, that study was limited by certain methodological considerations, so it was a single-arm study, unlike in the Phase III studies where there was a very rigorous case definition defined by PCR, and in the case where PCR could not be performed by the HZ/su, these were suspected cases that were then reported by the investigator on the case report form. So what we have about these cases are some clinical details, which in some cases are difficult to interpret.

We also have accumulating information in the extension studies that I mentioned in the Phase III study. So we have continued our placebo subjects in an additional extension where they are offered the HZ/su vaccine and they are followed, and although they also are not undergoing the same diagnostic procedures, we have 286 individuals who were actually herpes zoster cases in the Phase III studies now enrolled in the trial and received vaccination. Of those, we have one suspected case. So we have some conflicting information, and so as Dr. Agger mentioned, this is really why we believe it's

important to study this in a more rigorous way.

DR. EDWARDS: Dr. Long.

DR. LONG: Do you know if the zoster, was it the same site of previous zoster, the same dermatome?

DR. MILLER: So maybe we can pull up the backup slide that defines the cases. And maybe to address your question, we've invited Dr. Myron Levin -- he was actually the chairman of our HZAC, so he did a lot of these adjudications through the course of the Phase III study, and he also looked at these Zoster-033 cases for us to help give us a more independent view on what these cases might represent.

So thank you, Dr. Levin.

DR. LEVIN: Myron Levin, University of Colorado School of Medicine and a paid consultant to GSK.

So I was able to look at all the data that was available on these patients, and yes, there were some patients that had recurrences in the same area; at least one person had it three times in the same area. And there were certain features that I looked at that I used to try to determine if this was a typical case. They had to do with whether it was recurrent, whether it was in the lumbar area, which is common for herpes simplex, how quickly it healed, and how extensive it was. And a number of the cases would not have made it, would not have been considered a positive case by the adjudication committee.

So I think we were very limited in the amount of

information that we had of these cases. I actually requested if we could get additional information, but all we eventually had is what's presented here.

DR. EDWARDS: Was there any PCR data in any of these patients?

DR. LEVIN: No, no.

DR. EDWARDS: Okay.

DR. LEVIN: No.

DR. EDWARDS: Yes, Holly.

DR. JANES: Following up on that, with regard to the diagnoses of zoster in the efficacy trials where you did have the PCR data, I noticed that there was an apparent imbalance in both trials with regard to the fraction of the cases that were definitively diagnosed based on the adjudication committee versus based on PCR, suggesting perhaps that there were more indeterminate PCR results in the vaccine versus placebo groups.

DR. AGGER: There were also a lot fewer cases.

DR. JANES: Right, a lot fewer cases. So was that -- do you believe that that's a real trend? Does that have implications for diagnosis of the breakthrough cases?

DR. MILLER: Well, so in the Zoster-006 trial, it's really difficult to say because in the primary analysis there were only six cases. But let me show you actually an overview of the adjudication of our suspected cases just to give you the full picture.

So in Zoster-006, and we'll discuss that first, there were 84 suspected cases in the HZ/su group, 340 in the placebo group. Of those -- and here now, we're not talking about the primary efficacy analysis, we're talking about that second analysis that was performed at the very end of both of the pooled studies. By that time there were nine cases. Of those, 7 were confirmed by PCR, 2 of them were confirmed by the HZAC, and 75 of them were confirmed as not cases, and of those, again, the majority were PCR confirmed versus HZAC confirmed. If you then look at the placebo group, you have a much higher proportion of cases that were confirmed as yes, so about 75% overall. Of those, about 65% are PCR confirmed and 10% are HZAC confirmed, and of those no, still, PCR is confirming the majority of the cases. A similar pattern we're seeing in Zoster-022, and you can see the data listed there.

DR. EDWARDS: Are there any other questions? Yes.

DR. LONG: You're looking reluctant to give me the microphone. No, you're not reluctant.

DR. EDWARDS: If you have a question, please ask it.

DR. LONG: Okay. It's concerning the time frame of looking especially for cerebrovascular events, vasculopathies, etc., both in children with varicella and adults with strokes following zoster vaccines, either of them. The risk was increased through 6 months, so we don't know if it's -- I think it's unlikely that the virus is still there. It could be the

inflammatory response or something that the inflammatory response did early that makes one predisposed a little bit later. So I don't think our usual rules of 30 days for reactogenicity or adverse events, especially with live virus vaccines or different kinds of kill virus vaccines, may apply here, so I think the time frame is longer.

DR. AGGER: I think my SMQ analysis went from Month 0 to Month 8, which would comprise 6 months after last vaccination.

DR. EDWARDS: So any other last questions? I'm happy to have any more questions.

(No response.)

DR. EDWARDS: Okay. If not, then we've come to the period for the Open Public Hearing. Before that occurs, I would like to read about the Open Public Hearing.

Welcome to the Open Public Hearing. Please note that both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes it's important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information includes the sponsor's

payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have such financial relationships. If you choose not to address the issue of financial relationships at the beginning of the statement, it will not, however, preclude you from speaking.

Are there any speakers who will be talking today at the Open Public Hearing?

Okay, Dr. Polanin.

DR. POLANIN: Thank you for the opportunity to speak today. My name is Dr. Megan Polanin. I am a Senior Fellow at the National Center for Health Research. Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policy makers. We do not accept funding from industry, so I have no conflicts of interest.

An effective shingles vaccine is important for public health. As patients get older, they are more likely to develop long-term pain or postherpetic neuralgia as a complication of shingles. This pain can be severe and chronic. There is no cure, and treatments do not reliably relieve pain for all patients. The only way to reduce the risk of developing shingles and PHN is to get vaccinated.

Like any public health strategy, a vaccine's benefits must

outweigh its risks. Based on available research, Shingrix has displayed significant benefits compared with the current shingles vaccine on the market. Shingrix showed much higher levels of vaccine efficacy than the current shingles vaccine.

Zostavax only reduces the occurrence of shingles by about half for patients 60 or older, and its effectiveness declines as patients age. For patients 80 and older, Zostavax is only 18% effective.

Shingrix has displayed efficacy in preventing PHN in patients 50 years and older by preventing shingles. Zostavax is less effective in preventing PHN because it is less effective at preventing shingles. For people who were vaccinated and still developed shingles, Zostavax helped to reduce the duration of PHN but not the severity of pain. Shingrix can potentially be administered to vulnerable patients with weakened immune systems. Zostavax is a live attenuated vaccine and therefore is not safe for people with weakened immune systems, such as patients who have had radiation or chemotherapy and those with HIV.

Shingrix requires two doses while Zostavax is a one-time injection; however, that is a small price to pay for a much more effective vaccine.

Post-licensure studies are critical as we need long-term data to evaluate Shingrix's long-term efficacy for patients 50 years and older. This is especially relevant since Zostavax

may no longer be effective 8 to 11 years after vaccination. The company's proposed long-term follow-up studies will help to determine whether Shingrix is able to protect older adults from contracting shingles as they age. It is essential that those studies be completed in a timely manner and that the company provide adequate incentives to patients to stay in the study.

We do have some concerns about risks. Patients treated with Shingrix had a higher rate of common adverse events such as pain, swelling, and fatigue. In addition, one serious adverse event, supraventricular tachycardia, was reported more frequently for patients vaccinated with Shingrix compared with patients who had not during a 30-day post-vaccination period.

We are also concerned about optic ischemic neuropathy, which was reported within 30 days by two patients, within 2 months by another patient, and not reported at all in the placebo group. These issues warrant further attention.

For that reason, we agree with the company and FDA reviewers that continued pharmacovigilance is critical to evaluate adverse events for patients vaccinated with Shingrix compared to those vaccinated with Zostavax and those with placebo. This should include uncommon adverse events observed soon after vaccination and any other adverse events that may arise with larger sample sizes and longer-term studies.

We concur with the FDA's request that the company specifically address risks of inflammation from the vaccine,

which can lead to some of the adverse events reported during pre-licensure studies.

We urge this Advisory Committee to recommend that the FDA require critical post-approval long-term studies to further evaluate the efficacy and safety of Shingrix. We also strongly recommend that the company conduct subgroup analyses to ensure that the vaccine is safe and effective for both women and men and also people of color.

Thank you for the opportunity to share our perspective.

DR. EDWARDS: Thank you very much.

Okay, I think we now need to take some votes here and discuss the questions first and then vote. So could we have the first slide, the first question?

Are the available data adequate to support the efficacy of Shingrix for the prevention of herpes zoster in adults 50 years of age or older?

Let's go around the table and discuss this. Would you like to start for us, Dr. Bok?

DR. BOK: I think this is very clear. It's a lot better than the vaccine we have now. So the use of an adjuvant seems to do the trick and especially now that population, the older you get. So that's all.

DR. EDWARDS: Dr. Kotloff.

DR. KOTLOFF: I think that the data, there are very strong data. My one concern about a gap is the small amount of data

in people of color and Hispanics, and I think further studies would be very important in looking at those groups.

DR. EDWARDS: Dr. Lynfield.

DR. LYNFIELD: I agree.

DR. EDWARDS: Dr. Long.

DR. LONG: No concerns about efficacy.

DR. EDWARDS: Dr. Janes.

DR. JANES: No concerns about efficacy, albeit the previous points being made about it being unclear about efficacy in individuals with prior zoster.

DR. EDWARDS: Certainly, from my perspective, I think the adjuvant markedly enhances the efficacy in ways that are really quite impressive. The long-term duration and stability of the CMI responses and the antibody, for as long as it's been looked at, I think is also quite impressive.

Dr. Englund.

DR. ENGLUND: Yes, I'm very impressed by the efficacy, and those of us who have worked with shingles really are -- I mean, I am impressed, and I know that others would be impressed very much with the efficacy. Thank you.

DR. EDWARDS: Dr. Wharton.

DR. WHARTON: Yeah, I agree with what others have said. I think the data strongly support efficacy in the populations that were studied. There still are some populations that were not necessarily so well covered by the clinical trials, the

principal clinical trials that were presented, especially the more diverse population that we see in the United States.

And there also is this question about people who previously had zoster. I know that wasn't the primary target of the principal studies, but there remained some unanswered questions there.

DR. EDWARDS: Dr. El Sahly.

DR. EL SAHLY: The data presented do support the efficacy within the constraint of the population selected, i.e., no immune compromise, no previous zoster, etc., and for the duration of 4 or 5 years.

DR. EDWARDS: Dr. Sawyer.

DR. SAWYER: I agree with my colleagues and including the concerns about underrepresented populations.

DR. EDWARDS: Mr. Toubman.

MR. TOUBMAN: Agree. And I have a suggestion on that last point, which is that it seems like -- that's why I asked the question of Dr. Agger, if this is common that there's such low incidence of Africans and African Americans in the studies. One suggestion might be that the FDA could require that there be a more representative percentage if you're going to -- when you come before the Agency. I don't know if that's within our purview or not, but I think it would be helpful.

DR. EDWARDS: Dr. Greenberg, would you like to comment?

DR. GREENBERG: Thank you, yeah. I agree with the others

around the table, and I think it's a major advance with regard to the efficacy that we've seen today in the population with some limitations, but clearly, a major advance.

DR. EDWARDS: Okay. So it looks, unless other people would like to make any comments, that we're ready to vote, then.

Just to read the question: Are the available data adequate to support the efficacy of Shingrix for the prevention of herpes zoster in adults 50 years of age and older?

Yes, no, or abstain.

If we can push the button now? It's blinking, so I think we can.

(Committee vote.)

DR. EDWARDS: So it appears that we have 11 yeses and no abstains and no noes. We will read the individuals that have voted for or with yes.

Mr. Toubman, Dr. Sawyer, Dr. El Sahly, Dr. Wharton, Dr. Englund, Dr. Edwards, Dr. Janes, Dr. Long, Dr. Lynfield, Dr. Kotloff, and Dr. Bok.

Okay, so now we will put up the second question, and the question is: Are the available data adequate to support the safety of Shingrix when administered to adults 50 years of age and older?

Let's start on this end this time.

Dr. Greenberg.

DR. GREENBERG: My interpretation of the data are that the recognized increases in solicited injection site and systemic reactions are what they are, and they're short-lived and generally reasonable. And it's a risk-benefit analysis in my view, so an increase in short-term reactions in that risk-benefit analysis are fine, in my opinion.

And then some of the other more fine points around some of the events that were occurring, I think those are subjects of long-term pharmacovigilance, and I'm sure those can be evaluated over time.

DR. EDWARDS: Mr. Toubman.

MR. TOUBMAN: I agree with what was just said. I don't know that the pharmacovigilance program, how rigorous it is, but it certainly seems that all of the issues that were identified warrant very careful review.

DR. EDWARDS: Dr. Sawyer.

DR. SAWYER: Yes, I agree with Dr. Greenberg's summary. The adverse event profile is very well clarified for us, and we know it going in, and so I think the ongoing studies will illuminate the rarer event.

DR. EDWARDS: Dr. El Sahly.

DR. EL SAHLY: I agree about -- with what Dr. Greenberg just said.

DR. EDWARDS: Dr. Wharton.

DR. WHARTON: Yeah, I agree with the statements that have

been already. I would like to comment on, it is great seeing clinical studies that include so many people who are in the age range that were included in these studies where comorbidities are so common, and underlying medical conditions and events which probably are unrelated to vaccination are inevitably going to occur during follow-up periods and require careful evaluation to make sure that we're not seeing important imbalances that actually reflect vaccine safety issues.

I think there's been a really thoughtful job done by both the Sponsor as well as by CBER in looking at a large amount of very complicated adverse event data, and I don't see anything in it that provides a high level of concern. But clearly it is going to be important going forward, and there will be many events that occur post-vaccination that will have to be evaluated in the context of post-licensure surveillance to evaluate, to make sure that we understand the safety profile.

DR. EDWARDS: Dr. Englund.

DR. ENGLUND: I agree. I think doing vaccine trials in high-risk people, which this is, and which ongoing trials which we all are very excited about will be -- are very challenging, they're very challenging. And I think when we do enough comparative analysis of about 1,000 different data points, the fact that we found some significant factors -- they weren't even significant -- but some imbalances is to be expected, and I think that's very important.

I also would echo the comment that Dr. Sawyer made. This is good, patients need to know going into this, that there is a chance of some short-lived reactions. We know that they need to be advised of that by their care provider. But I believe the answer to Question 2 is yes.

DR. EDWARDS: Certainly, I applaud the comprehensive analysis of all of these safety signals, and as Melinda said, I think that both the Sponsor and FDA have done a really wonderful job of really digging down and trying to answer the questions.

And I also think it is reassuring that 006 and 022 sort of had -- some of the adverse events were reversed in the vaccine and the control groups in the two studies and making me think that maybe it's the gremlins of randomization and not really the gremlins of adverse events. So, certainly, we need to have post-licensure surveillance as has been outlined, but I think that the plan for post seems very adequate.

Dr. Janes.

DR. JANES: Yeah, I'm in full agreement with the prior comments. Nothing further to add.

DR. EDWARDS: Dr. Long.

DR. LONG: Well, I think I've been a little bit swayed by listening to starting on the other side of the room because I think this is a very good case for the first licensure of this adjuvant in the United States because the efficacy seems pretty

compelling, the disease is morbid, and there are a lot of people whose lives can be changed. But it is inducing the host to make an inflammatory response that they otherwise wouldn't be making. So it is different, it is unusual, and I wish there were more safety data in the United States with the kind of risk people that we have for some of the concerns that there are regarding safety.

So I think it is, with the data that we have at hand, do we have enough information that the potential benefits outweigh the concerns of risk? And I'm going to maybe decide that as we finish the table.

DR. EDWARDS: Dr. Lynfield.

DR. LYNFIELD: I agree with, I think, the comments that people have made. I think that it is a difficult thing to do to study people in this age group. It is a very morbid disease, and I think that we do have data that show that it is safe. I think it makes sense to have a pharmacovigilance plan going forward for all the reasons everyone has already articulated. We need to really ensure that the safety is there, we need to look at additional populations, and I am comfortable with the plan that's in place.

DR. EDWARDS: Dr. Kotloff.

DR. KOTLOFF: Yes, thanks. So I would like to echo the congratulations to the company and to CBER on taking this huge body of data and analyzing it and presenting it so clearly.

I think that the future, part of the future of vaccines is that we're going to see more powerful adjuvants and that we're going to be vaccinating more vulnerable populations, and so there may be new reactogenicity that we don't understand that we're going to have to very carefully look at. So I think that the -- you know, I just want to emphasize the importance of a very carefully thought out pharmacovigilance plan.

And particularly with regard to SVT, I'm not a cardiologist, but there may be differences in the ability of an adjuvant to trigger atrial fib and SVT, and so I think that that also has to be carefully looked at so we don't dilute a signal by lumping it together with potentially unrelated factors.

DR. EDWARDS: Dr. Bok.

DR. BOK: Yes, I believe the answer is yes. I am going to join on the congratulations. I think it's a great study, especially on immunosenescence and immunosenescent populations. For me, the safety profile is strong, and it's either strong or it's going to be addressed with the pharmacovigilance plan.

The only question I have is following up. I was also confused by the 033, which is a little bit -- the results are not clear, and it would be nice to see, once the herpes zoster cases are confirmed, to see those people vaccinated and follow the safety profile and especially keeping in mind how long after the episode you're going to vaccinate them and what's the

safety after that. So, for me, that's the only thing I would like to just comment on.

DR. EDWARDS: Okay, thank -- Dr. Greenberg.

DR. GREENBERG: Sorry, I just wanted to get back to a comment that was made a couple times today. My background, like yours and many, are in pediatric infectious diseases, so that's where I did most of my clinical trials prior to industry, where, you know, you pretty much put your study investigators in areas in the country and in populations where there are diverse individuals and you'll get a diverse study population. It is different in seniors. For a variety of social and other reasons, they tend not to participate in these types of trials or in vaccine trials in general. It is a big challenge. I don't have a solution, and I don't question that we should question, you know, how to get that done and have a more diverse population in our senior trials, but it's not easy. It's not just a matter of choosing investigators in the right places.

DR. EDWARDS: Thank you. Well said.

Okay, any other comments?

(No response.)

DR. EDWARDS: Okay. So the question is: Are the available data adequate to support the safety of Shingrix when administered to adults 50 years of age and older?

So vote yes, no, or abstain.

(Committee vote.)

CAPT HUNTER-THOMAS: Okay, so the total is 11 yes, zero abstain, and zero no.

And we will read the names individually for the record starting with Dr. Bok, yes; Dr. Kotloff, yes; Dr. Lynfield, yes; Dr. Long, yes; Dr. Janes, yes; Dr. Edwards, yes; Dr. Englund, yes; Dr. Wharton, yes; Dr. El Sahly, yes; Dr. Sawyer, yes; Dr. Toubman, yes.

Thank you.

DR. EDWARDS: Are there any other comments that FDA would like to make?

DR. GRUBER: Let me confer real quick with my colleagues here, just a little glance back. Yes, I was confirmed that we are all good, and I really want to thank the Committee for the deliberations; it was really helpful. And yeah, that's all, I think. We're going to continue working with the Applicant on this file.

DR. EDWARDS: Thank you, thank you.

Did you have a comment, Mr. Toubman?

MR. TOUBMAN: Yes, I did actually have a question, which is that in the situation where it's been discussed where for people who have already had the disease, zoster, there's a study that's -- it's unclear, you know. Is this a thing -- is this a situation where FDA, in the approval, in the license, makes a comment about that, or how does that work in terms of

educating clinicians that there's an issue there?

DR. GRUBER: So we have actually means of describing a certain data or lack thereof in the package insert, so I think we're going to be discussing how we're going to be describing this. So you were referring to those people that had previous herpes zoster and, you know, what happens to them if they're going to be vaccinated with Shingrix. Yeah, I mean, as you heard, the Applicant is going to do a study, you know, to look into this further, so right now I can envision the package insert that there are no data on this at this time. But, again, this is something that we're still going to be discussing on how we include or not include such information or data in the package insert.

DR. EDWARDS: Thank you.

And thank you, members of the Committee. Thank you, members for the audience, those on the webcast, and certainly thank you to the Applicant for an excellent presentation.

(Whereupon, at 2:14 p.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

148TH MEETING OF THE VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

September 13, 2017

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Biologics Evaluation and Research.

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TOM BOWMAN

Court Reporter