

UNITED STATES OF AMERICA
 DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

+ + +

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

+ + +

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
JANET ENGLUND, M.D.	Voting Member
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

This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

Free State Reporting, Inc.
 1378 Cape St. Claire Road
 Annapolis, MD 21409
 (410) 974-0947

FDA ADMINISTRATIVE STAFF

CAPT SERINA HUNTER-THOMAS, M.S.A., RN
Designated Federal Officer
Vaccines and Related Biological Products Advisory Committee
Division of Scientific Advisors & Consultants
Center for Biologics Evaluation and Research

ROSANNA HARVEY
Committee Management Specialist
Vaccines and Related Biological Products Advisory Committee
Division of Scientific Advisors & Consultants
Center for Biologics Evaluation and Research

FDA SPEAKERS/PARTICIPANTS

MARION GRUBER, Ph.D.
Director, Office of Vaccines Research and Review
Center for Biologics Evaluation and Research

CARMEN M. COLLAZO-CUSTODIO, Ph.D.
Microbiologist
Division of Vaccines and Related Product Applications
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research

JEFFREY COHEN, M.D.
Chief, Laboratory of Infectious Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health

PAULA AGGER, M.D., M.P.H.
Division of Vaccines and Related Product Applications
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research

SPONSOR SPEAKERS/PARTICIPANTS

KIMBER POFFENBERGER, Ph.D.
Vice President and Head
North American Regulatory Affairs
GSK Vaccines

BARBARA YAWN, M.D., M.Sc., FAAFP
Adjunct Professor
Department of Family and Community Health
University of Minnesota School of Medicine

ARNAUD DIDIERLAURENT, Ph.D.
Director and Head of Adjuvant Platform
Belgium R&D
GSK Vaccines

JACQUELINE M. MILLER, M.D., FAAP
Vice President and Head
U.S. Clinical R&D
GSK Vaccines

JENS-ULRICH STEGMANN, RN, M.D.
Vice President and Head
Clinical Safety and Pharmacovigilance
GSK Vaccines

LIDIA OOSTVOGELS
Director, Clinical and Epidemiology Project Leader
Clinical R&D
GSK Vaccines

MYRON LEVIN, M.D.
University of Colorado School of Medicine

OPEN PUBLIC HEARING SPEAKER

MEGAN POLANIN, Ph.D.
Senior Fellow
National Center for Health Research

INDEX

	PAGE
Call to Order - Kathryn Edwards, M.D.	6
Introduction of Committee	6
Administrative Announcements - CAPT Serina Hunter-Thomas, M.S.A., RN	8
Conflict of Interest Statement - CAPT Serina Hunter-Thomas, M.S.A., RN	9
Introduction and Presentation of Questions - Carmen Collazo-Custodio, Ph.D.	13
Epidemiology and Disease Burden of Herpes Zoster in Adults Aged 50 Years and Older - Jeffrey I. Cohen, M.D.	16
Q&A	35
Sponsor Presentations: GlaxoSmithKline	
Introduction - Kimber Poffenberger, Ph.D.	39
HZ Epidemiology and Burden of Disease - Barbara Yawn, M.D., M.Sc., FAAFP	42
Q&A	50
Vaccine Design and Scientific Rationale - Arnaud Didierlaurent, Ph.D.	51
HZ/su Clinical Efficacy Data and HZ/su Immunogenicity - Jacqueline M. Miller, M.D., FAAP	60
HZ/su Safety - Jens-Ulrich Stegmann, RN, M.D.	74
Conclusions - Jacqueline M. Miller, M.D., FAAP	88
Q&A	91
FDA Presentation	
Herpes Zoster Vaccine (Recombinant), Adjuvanted (SHINGRIX): Review of Efficacy and Safety - Paula Agger, M.D., M.P.H.	121
Q&A	151

INDEX

	PAGE
Open Public Hearing	
Megan Polanin, Ph.D.	171
Committee Discussion and Vote	174
Adjourn Meeting	185

M E E T I N G

(8:34 a.m.)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

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.

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

4 Ruth.

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

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

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

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

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

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

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

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

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

8 DR. EDWARDS: Thank you very much.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 At this meeting there may be regulated industry speakers

1 and other outside organization speakers making presentations.
2 These speakers may have financial interests associated with
3 their employer and with other regulated firms. The FDA asks,
4 in the interest of fairness, that they address any current or
5 previous financial involvement with any firm whose product they
6 may wish to comment upon. These individuals were not screened
7 by the FDA for conflicts of interest.

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

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

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

21 Thank you.

22 DR. EDWARDS: Thank you very much.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 And this concludes my presentation. Thank you for your

1 attention.

2 DR. EDWARDS: Thank you.

3 Are there any questions?

4 (No response.)

5 DR. EDWARDS: Thank you.

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

10 Jeff.

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

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

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

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

4 So if one looks at individual neurons in healthy
5 individuals who've had chicken pox years later in life, and we
6 looked at over 1,700 in our laboratory, you can see that about
7 4% of the neurons are positive for varicella zoster virus, and
8 the average copy number of VZV was about seven copies per
9 neuron.

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

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

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

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

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

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

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

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

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

4 So, again, the rash is usually in a dermatomal pattern,
5 does not cross the midline, can involve two or three dermatomes
6 in healthy individuals, and it's not uncommon to see a few
7 lesions outside the dermatome probably associated with a low
8 level of viremia seen in healthy individuals. The rash is more
9 common in certain ganglia, such as thoracic and lumbar. New
10 lesions occur over 5 to 7 days, and crusting takes up to about
11 12 days. And some patients, rare patients, don't have a rash
12 but will have pain, referred to as zoster sine herpete.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

16 So in terms of economic burden of zoster, one of the best
17 studies was done by Barbara Yawn, who I think is here today,
18 and this was a study done, carried from 1996 to 2001 in
19 Olmstead County, Minnesota, and you can see that of patients
20 with zoster, the mean cost to treat per patient was about
21 \$1,300. This increases about three and a half to fourfold if
22 one has postherpetic neuralgia, and it increases further if one
23 has complications associated with zoster, including ocular
24 complications, neurologic complications, dermatologic
25 complications, or other complications such as disseminated

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

2 Now, if one is treating immunocompromised patients, again,
3 the increase -- there's a further increase in the average cost
4 per patient of \$3,600 per case. And this study involved about
5 1,700 individuals in Olmstead County. About one-tenth of them
6 had PHN, and about a tenth of them had non-pain complications.

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

14 So additional data from that paper shows the percent of
15 cost due to hospitalization, and you can see that patients who
16 have complications accounted for about 50% of the
17 hospitalization costs; those with PHN, about 40% of
18 hospitalization costs; and those without complications, about
19 15%. And, again, if one looks at the costs broken down by
20 hospitalizations, emergency department visits or outpatient
21 visits, again, most of the costs are associated with outpatient
22 visits, particularly in those with postherpetic neuralgia or
23 complications compared to those without postherpetic neuralgia.
24 But there are also costs, of course, due to emergency room
25 visits and just outpatient, no hospitalizations.

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

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

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

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

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

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

1 average cost per zoster patient, if you look at all ages, is
2 about \$1,100. And, again, in the prior study, it was about
3 \$1,300, so the numbers are quite similar here, despite the fact
4 that these studies were done in difference in time and
5 different methodology here.

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

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

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

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

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

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

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

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

1 been shown to reduce the pain associated with postherpetic
2 neuralgia.

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

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

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

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

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

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

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

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

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

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

5 Again, for the Shingles Prevention Study, these
6 individuals were 4.9 years after vaccination with a mean
7 follow-up of 3.1 years. The same individuals were followed an
8 additional period of time for a mean follow-up between 3.3 and
9 7.8 years in the Long-Term Persistence Study here, with a mean
10 follow-up of 3.7 years. The efficacy did decline over time:
11 51% to 40% to 21%.

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

17 There's also been a study of the zoster vaccine in
18 individuals 50 to 59, rather than the Shingles Prevention
19 Study, which were individuals over age 60. Here you can see
20 individuals were followed for up to 2 years after vaccination
21 for a mean follow-up of 1.3 years, and the efficacy was about
22 60% in the ZEST trial.

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

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

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

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

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

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

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

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

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

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

16 So the vaccine is currently approved for individuals aged
17 60 and above or based by the ACIP, and it's licensed by FDA for
18 individuals 50 and above.

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

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

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

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

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

22 So, in summary, without the vaccine, 50% of persons aged
23 85 will get zoster. The rate of zoster is increasing.

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

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

2 The frequency of zoster and PHN increase with age.

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

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

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

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

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

20 Are there questions? Dr. Long.

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

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

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

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

8 DR. COHEN: Um-hum.

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

16 And I'm also wondering a little bit, with decreased
17 likelihood of silent re-exposures because of decreasing in
18 varicella, if we're going to see 50-year-old people in the next
19 10 years who are going to start at a different point, asking
20 different things of the vaccine. And do you have anything to
21 say about any of that?

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

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

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

15 DR. EDWARDS: Dr. Greenberg.

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

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

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

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

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

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

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

24 DR. COHEN: Thank you for keeping me honest.

25 DR. LONG: Thank you.

1 DR. EDWARDS: Other questions?

2 (No response.)

3 DR. EDWARDS: Thank you very much, Jeff.

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

6 UNIDENTIFIED SPEAKER: Move on.

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

11 Good morning. Go ahead. Thank you.

12 DR. POFFENBERGER: Thank you.

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

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

25 Dr. Arnaud Didierlaurent, head of the GSK Adjuvant

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

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

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

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

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

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

1 in our presentation as HZ/su.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18 But with increasing age, VZV-specific immunity, especially
19 cellular immunity, declines. At some point, usually after age
20 45 to 50, the VZV-specific immunity falls below the
21 hypothesized immunological threshold -- that's the dashed
22 line -- and zoster may occur. Zoster vaccine and vaccination
23 is designed to push immunity back above this threshold.

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

1 older. In this slide you see the incident rate of zoster in
2 each decade of adulthood, as well as the rates of postherpetic
3 neuralgia, in orange, and you can see they go from less than
4 10% up to almost a quarter or a third of those in the oldest
5 age group that have postherpetic neuralgia. You'll notice that
6 the increase incidence begins before 50, not just in the oldest
7 old, and it continues increasing throughout life. As the
8 population ages, the annual 650,000 cases in adults 50 years
9 and older are likely to increase, adding to the burden of
10 zoster pain and complications.

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

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

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

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

14 Patients often describe this acute pain as at least a 4 to
15 7 out of 10, pain comparable to kidney stones or even the late
16 stages of labor but without the waxing and waning of labor
17 pains. The pain usually lasts until the rash heals or beyond
18 for several weeks. At 90 days we label this pain as PHN, or
19 postherpetic neuralgia, which then may continue for many more
20 months. Eighty percent of PHN does resolve within 12 months.
21 But for one in five people with PHN, especially the oldest,
22 this will continue with daily pain for more than a year,
23 greatly impacting their quality of life, ability to engage in
24 self-care, markedly limiting family, social, hobby, or work
25 activities. Try to imagine the impact of pain that keeps you

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

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

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

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

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

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

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

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

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

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

1 recent Cochrane collaborative review.

2 Shingles is associated with major morbidity, and treatment
3 is inadequate at all stages. Prevention seems to be a much
4 better option. And prevention is now possible with a currently
5 approved zoster vaccine. Approval of Zostavax was a very
6 important addition to my clinical practice about shingles.
7 However, the efficacy of that vaccine is limited, beginning at
8 about 70% when vaccinating 50- to 59-year-olds and falling to
9 18% when vaccinating those 80 and older, as shown in this table
10 from the Zostavax PI.

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

19 So, with zoster, we're left with several opportunities for
20 improvement. We have a common condition, more than a million
21 cases a year. Almost all adults over the age of 40, more than
22 99%, are seropositive for VZV and therefore at risk of
23 shingles; one of three of them will get shingles.

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

1 greatest risk of zoster, its pain, and complications.

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

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

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

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

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

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

18 Okay, Karin. Dr. Bok.

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

22 DR. YAWN: Yes.

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

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

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

6 DR. BOK: Yeah, yeah.

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

12 DR. BOK: Yeah.

13 DR. YAWN: -- as we move forward?

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

17 DR. BOK: Those are certainly considerations, yes.

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

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

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

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

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

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

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

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

1 considered to be important.

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

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

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

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

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

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

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

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

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

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

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

1 groups and populations.

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

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

20 I will next briefly summarize the key principles on the
21 mechanism of action of AS01. First, shortly after injection,
22 AS01B components are recognized by specific -- sorry, by
23 specific pathways of innate immunity, namely toll-like receptor
24 4 for MPL and caspase-1 for QS-21. The target cells of AS01B
25 are macrophages in the draining lymph node.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18 Finally, we investigated in this study the immune response
19 after one or two doses. In blue are the data showing two dose
20 schedules of 50 µg gE and AS01B, and this is the current
21 formulation of HZ/su. The red line is one single dose of
22 100 µg gE in AS01B given after saline. Both antibody and
23 cellular response were significantly higher after two doses as
24 compared to one dose. This difference was maintained
25 throughout the study period and, again, regardless of age.

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

4 In this study, we compared AS01B with its half formulation
5 AS01E, as described at the top of the table. As shown in
6 Zoster-03 study, adding AS01, whatever the dose, enhanced the
7 CMI and antibody response when compared to gE alone, as you can
8 see in the first column. When compared head to head,
9 formulation of gE with AS01B significantly increased the number
10 of gE-specific CD4 T cells by 30% and gE antibody response by
11 40%. This was seen across all age groups. So these results
12 confirm the choice of AS01B as the adjuvant that induces the
13 highest immune response VZV in order to maximize the vaccine
14 capacity to prevent shingles long term.

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

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

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

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

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

3 DR. MILLER: Thank you, Dr. Didierlaurent.

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

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

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

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

25 The most important studies in our development program are

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

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

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

13 There were some additional Phase III studies which were
14 conducted. These included Zoster-026, which demonstrated that
15 a second dose of HZ/su can be given 2 to 6 months after the
16 first; Zoster-004, a co-administration study with influenza
17 vaccine; Zoster-007, a lot-to-lot consistency study; Zoster-
18 033, where HZ/su was administered to patients who previously
19 reported herpes zoster; and Zoster-032, which investigated
20 subcutaneous administration.

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

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

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

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

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

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

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

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

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

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

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

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

1 cases and enabled a more robust estimate of efficacy.

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

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

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

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

25 Approximately 85% of those enrolled had at least one

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

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

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

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

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

25 If at least one of the three lesion samples was positive

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

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

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

15 A case decided by the HZAC had to be confirmed as yes or
16 no by a unanimous vote. If one or more members were unable to
17 decide, or the yes/no decisions were not unanimous, the case
18 was not confirmed. The concordance between the HZAC assessment
19 and PCR results, when they were available, was approximately
20 90%.

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

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

7 Study 006 met its primary endpoint with vaccine efficacy
8 of 97.2% for subjects greater than or equal to 50 years of age.
9 The lower limit of the 95% confidence interval was 93.7%. The
10 statistical criterion defining efficacy was a lower limit of
11 25%, so the primary hypothesis was met. The HZ/su group
12 experienced a reduction in herpes zoster incidence from 9.1 to
13 0.3 per 1,000 person-years.

14 In each of the pre-specified age strata, 50 to 59, 60 to
15 69, and greater than or equal to 70 years of age, the observed
16 vaccine efficacy was between 96.6 and 97.9%.

17 In addition, as shown in the sentence below, the
18 observed -- an analysis was added to the statistical plan to
19 align with the current ACIP recommendation to vaccinate adults
20 over 60 years of age. The vaccine efficacy in this group was
21 97.6%.

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

1 needs for herpes zoster.

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

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

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

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

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

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

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

23 The efficacy against PHN in those over 50 years of age was
24 91.2%, and the same statistical criterion was met with a lower
25 limit of the 95% confidence interval well above zero. Note

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

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

7 There were six additional complications of herpes zoster
8 specifically captured in this study: ophthalmicus, disseminated
9 disease, visceral disease, vascular disease, neurologic
10 disease, and stroke. When we compiled all of these data
11 together in a post hoc analysis, we found that the efficacy
12 against herpes zoster-related complications other than PHN was
13 93.7% in those greater than 50 and 91.6% in those greater than
14 70 years of age, consistent with the other estimates of vaccine
15 efficacy in these studies.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 of antibody in both groups.

2 Once again, you see that there was a rapid increase in
3 antibody concentrations in the HZ/su group to 42-fold over
4 baseline values after the second dose, plateauing after the
5 first year and maintained at ninefold above baseline values
6 3 years after vaccination.

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

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

13 Although persistence results are not yet available from
14 the subsequent time points of the Phase III studies, we do have
15 persistence data from one of the earlier clinical studies. The
16 extension study, Zoster-024, involved continued follow-up of
17 subjects from the antigen dose ranging study, Zoster-003, in
18 which subjects were originally vaccinated when they were
19 greater than or equal to 60 years of age. Dr. Didierlaurent
20 already presented the immunogenicity data through Year 3 from
21 this study. These subjects were followed for an additional
22 3 years to look at the persistence of CMI in humoral responses.

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

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

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

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

20 DR. STEGMANN: Thank you, Dr. Miller.

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

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

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

6 Safety data for over 17,000 recipients of HZ/su were
7 included in the submission to the FDA. In Zoster-006 and -022,
8 more than 14,000 subjects received HZ/su, which represents over
9 85% of the safety database. This presentation will focus on
10 the main safety pooling, a pre-specified analysis conducted on
11 the pooled datasets of Zoster-006 and Zoster-022. This is
12 because of the similar design of the two studies, as already
13 outlined by Dr. Miller, and the ability to compare to a placebo
14 control.

15 Solicited symptoms, which include injection site reactions
16 and common general reactions which occur in proximity to the
17 vaccination, were assessed in a diary card subset of nearly
18 10,000 subjects. There were approximately 5,000 subjects each
19 in the HZ/su and placebo groups.

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

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

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

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

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

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

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

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

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

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

16 This slide presents the solicited general symptoms
17 reported in the diary card subset. As listed from left to
18 right is fatigue, fever, gastrointestinal symptoms, headache,
19 myalgia, and shivering. Fatigue, headache, and myalgia were
20 the most frequently reported symptoms in both groups, with
21 HZ/su group reporting symptoms more frequently than the placebo
22 group. The majority of these reactions were mild to moderate
23 in severity, and the median duration was less than or equal to
24 2 days in the HZ/su group.

25 These are the corresponding Grade 3 solicited general

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

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

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

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

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

1 and not just the diary card subset.

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

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

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

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

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

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

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

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

14 Now, coming back to the SAEs, this is a statistical
15 comparison of the 10 most frequently reported serious adverse
16 event terms grouped in system organ classes, or SOCs, within
17 365 days of vaccination. These terms include infections such
18 as pneumonia, cardiac events, and neoplasm, as would be
19 expected in this population of adults greater than or equal to
20 50 years of age.

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

1 which the p-values were all non-significant.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

15 This slide summarizes a few imbalances or cases identified
16 in the HZ/su program that were considered noteworthy by the
17 FDA. These events will be monitored in the proposed
18 pharmacovigilance plan. This table gives information on the
19 three time periods analyzed for the 30-day time period serious
20 adverse events and unsolicited AEs were captured, while in the
21 365-day time period and the entire study period only SAEs were
22 captured.

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

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

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

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

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

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

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

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

3 Supraventricular tachycardia: The imbalance seen in the
4 365 days after vaccination does not appear in a more targeted
5 analysis focusing on all supraventricular arrhythmia.
6 Nevertheless this, as other relevant cardiac events, will be
7 captured in the active surveillance.

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

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

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

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

1 of a specific report.

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

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

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

15 The follow-up period per subject is aimed to be at least
16 12 months after vaccination. And this study is currently under
17 discussion with the FDA.

18 So, to summarize our safety findings, over 17,000 adults
19 received HZ/su during the development program, and more than
20 14,000 received at least one dose of HZ/su in the two pivotal
21 Phase III safety and efficacy trials, and an approximately
22 equal number of subjects received placebo.

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

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

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

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

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

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

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

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

21 DR. MILLER: Thank you, Dr. Stegmann.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 Other questions? Yes, Sheldon.

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

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

13 MR. TOUBMAN: Thank you.

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

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

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

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

7 DR. EDWARDS: Perhaps --

8 MR. TOUBMAN: Sorry.

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

10 MR. TOUBMAN: Oh, I'm sorry.

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

13 MR. TOUBMAN: Okay.

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

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

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

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

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

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

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

13 DR. EDWARDS: Please, go on.

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

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

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

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

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

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

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

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

1 how common that is for the current vaccine.

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

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

15 And, again, these are the same subjects in the antigen
16 dose ranging study. These subjects have now, beyond the
17 Zoster-024 6-year persistence time point, been followed out to
18 9 years, and again, you see the cell-mediated immunity on the
19 left and you see the humoral response on the right, and we see
20 that the plateau continues to be maintained.

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

1 of the subjects in the Phase III studies for efficacy.

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

8 MR. TOUBMAN: Thank you very much.

9 DR. EDWARDS: Good questions.

10 Dr. Long.

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

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

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

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

22 DR. LONG: Yes, yes.

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

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

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

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

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

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

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

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

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

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

1 related to the vaccination for those events.

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

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

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

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

15 DR. LONG: Yes.

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

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

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

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

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

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

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

6 DR. LONG: And do I remember, then, that that's about
7 14,000? These numbers are of 14,000?

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

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

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

17 DR. OOSTVOGELS: Lidia Oostvogels from the clinical team.

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

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

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

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

10 DR. OOSTVOGELS: It's C-6.

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

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

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

22 So when we looked at the U.S. and Canada, for example, the
23 African Americans are more reflected. And if we looked in the
24 U.S. population alone, actually, the number increased to about
25 8%, so getting at least a little bit closer to the general

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

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

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

10 DR. EDWARDS: Holly.

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

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

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

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

1 that we have ongoing.

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

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

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

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

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

1 vaccine.

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

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

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

16 And I can also show you next the progression between the
17 HZ/su group and the placebo group from the total vaccinated
18 cohort to the modified total vaccinated cohort. This is from
19 the Zoster-006 study, but the results are also similar in the
20 -022 study.

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

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

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

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

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

19 DR. EDWARDS: Dr. Sawyer.

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

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

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

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

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

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

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

1 subjects received two doses in the Phase III trials, and
2 therefore, most of these subjects, either they were part of the
3 5% that didn't receive a second dose or these were individuals
4 who had their case of herpes zoster occur prior to Day 30 post-
5 Dose 2, and therefore the average follow-up for an individual
6 was only about 80 days post-vaccination, so sample size and
7 duration of follow-up are limited.

8 Nonetheless, if you look in the top row, that's analogous
9 to the Zoster-006 analysis in those greater than or equal to
10 50; one-dose efficacy was 90.8%. And in the pooled analysis
11 for those greater than or equal to 70, that's at the bottom row
12 of the table, the one-dose efficacy was 69.5%.

13 DR. EDWARDS: Dr. Wharton.

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

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

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

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

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

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

14 DR. EDWARDS: Hana.

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

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

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

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

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

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

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

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

1 treatment of a chronic condition was an exclusion criterion.

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

6 DR. EDWARDS: Dr. Englund.

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

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

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

1 on a relative number, it's the other way around, as well for
2 365 days, that we don't see any relevance, a difference, with
3 the occurrence of these events.

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

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

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

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

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

4 DR. EDWARDS: Karen.

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

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

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

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

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

21 DR. KOTLOFF: Convulsions and SVT.

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

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

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

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

21 DR. KOTLOFF: And that supraventricular tachycardia?

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

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

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

9 DR. MILLER: Thank you, Dr. Stegmann.

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

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

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

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

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

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

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

1 And what I can say is that the study met its primary
2 objective, which was to demonstrate non-inferiority in terms of
3 the geometric mean antibody concentrations. And so here you
4 see the top line data from that study, so the GMC ratio was
5 1.04 with an upper limit of 1.17, and that was lower than the
6 predefined statistical criterion of 1.5.

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

11 DR. MILLER: Thank you for your suggestion.

12 DR. EDWARDS: Questions?

13 Sarah.

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

20 DR. MILLER: Sure.

21 DR. LONG: Do you have any information?

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

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

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

11 (Pause.)

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

19 DR. EDWARDS: Thank you.

20 Any other final questions?

21 Yes, David.

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

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

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

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

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

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

21 DR. MILLER: Yes, we did perform that analysis, and it was
22 a small, as you mentioned, proportion of the overall total. So
23 here are the solicited symptoms that were ongoing beyond the
24 7-day post-vaccination period.

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

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

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

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

12 DR. EDWARDS: One more.

13 DR. GREENBERG: -- before lunch?

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

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

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

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

15 DR. EDWARDS: Okay, thank you very much.

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

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

20

21

22

23

24

25

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

(12:30 p.m.)

1 DR. EDWARDS: Dr. Agger will begin.

2
3 DR. AGGER: Good afternoon, everyone. I'm Paula Agger. I
4 am a medical officer in the Office of Vaccines Research and
5 Review, CBER/FDA. I, along with my colleague, Dr. Rebecca
6 Reindel, was responsible for the clinical review of the data
7 submitted by GlaxoSmithKline in support of the licensing
8 application for Shingrix.
9

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 Non-ordinal solicited symptoms and unsolicited adverse

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

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

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

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

1 each clinically suspected case.

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

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

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

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

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

1 60 to 69, 70 to 79, and greater than or equal to 80 years of
2 age. Approximately 58% of subjects participated in the 7-day
3 diary card subset for the collection of solicited symptoms, and
4 all subjects greater than or equal to 70 years of age were
5 included in this subset.

6 The success criterion for the primary endpoint of
7 Zoster-006 would be met if the lower bound of the two-sided 95%
8 confidence interval for herpes zoster vaccine efficacy in
9 subjects greater than or equal to 50 years of age was above
10 25%.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11 After a median follow-up time of 3.1 years, there were six
12 subjects with confirmed cases of HZ in the mTVC of the Shingrix
13 group and 210 with confirmed HZ in the mTVC of the placebo
14 group. The incidence of HZ in the Shingrix group was 0.3 per
15 1,000 person-years, and the incidence of HZ in the placebo
16 group was 9.1 per 1,000 person-years. Calculated Shingrix
17 herpes zoster vaccine efficacy was therefore 97.16% with a
18 lower bound of the 95% confidence interval being 93.72%. The
19 primary efficacy success criterion for Zoster-006 was met, as
20 the lower bound of the 95% confidence interval for the point
21 estimate of herpes zoster vaccine efficacy was above 25%.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

15 Pain was the most commonly reported local symptom. The
16 proportions of subjects in the Shingrix group reporting at
17 least one any grade or Grade 3 local symptom was generally
18 comparable between Dose 1 and Dose 2. The median duration of
19 pain, redness, or swelling in the Shingrix group was about
20 3 days.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 This table presents the distribution of subjects by

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

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

10 94.3% and 95.2% of subjects in the TVC of the Shingrix and
11 placebo groups, respectively, were included in the mTVC for the
12 herpes zoster efficacy analysis in Zoster-022. Again, the
13 primary reason that subjects in the TVC were excluded from the
14 mTVC was due to not receiving two doses; 5.6 and 4.4% of the
15 Shingrix and placebo groups, respectively, didn't receive two
16 doses.

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

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

1 completed and withdrew were comparable between vaccination
2 groups.

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

9 This slide presents the numbers for analysis of the
10 primary herpes zoster efficacy endpoint. After a median
11 follow-up time of 3.9 years, there were 23 confirmed cases of
12 HZ in the mTVC of the Shingrix group and 223 in the mTVC of the
13 placebo group. The incidence of HZ in the Shingrix group was
14 0.9 per 1,000 person-years, and the incidence of HZ in the
15 placebo group was 9.2 per 1,000 person-years.

16 Calculated Shingrix herpes zoster vaccine efficacy was
17 89.79% with a lower bound of the 95% confidence interval being
18 84.29%. The primary study objective of Zoster-022 was
19 therefore met as the lower bound of the 95% confidence interval
20 for the point estimate of herpes zoster vaccine efficacy was
21 above 10%.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 Now we're going to discuss the results, the pooled
13 results, from the pivotal studies. There were two pooled
14 safety analyses: the main pooling, consisting of subjects in
15 Zoster-006 and Zoster-022, and the broader pooling analysis
16 which included an additional 848 subjects from several other
17 Phase II and III studies who received at least one dose of
18 Shingrix on a Month 0, Month 2 schedule and who had at least
19 1 year of safety follow-up post-vaccination prior to the data
20 lock point for safety analyses. Only SAEs, pIMDs, and deaths
21 were analyzed on this broader pooling.

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

25 This slide presents the proportions of subjects who

1 reported at least one SAE during select time periods
2 post-vaccination, which were comparable between vaccination
3 groups. In general, the proportions of subjects reporting
4 events by SOC and PT were also comparable, except for the
5 preferred term of supraventricular tachycardia, which was
6 reported by higher proportions in the Shingrix group during the
7 365-day post-vaccination period, six reports versus zero
8 reports. No difference between treatment groups, however, was
9 noted by CBER for events reported in the supraventricular
10 tachyarrhythmias SMQ for the pooled analysis for this period.

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

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

25 Additionally, while there is no standardized MedDRA query

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

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

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

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

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

4 One death was judged vaccine related by the investigator
5 but not the Applicant; this event is starred in the Shingrix
6 group on the left. The subject was greater than 90 years of
7 age with a past medical history of stable immune
8 thrombocytopenia for 10 years who was noted to be pancytopenic
9 72 days after Dose 1. He was diagnosed with acute myeloid
10 leukemia 3 days after the pancytopenia diagnosis and developed
11 neutropenic sepsis 97 days after Dose 1, dying 1 day later.

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

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

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

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

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

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

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

1 hyperhidrosis, and gout.

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

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

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

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

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

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

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

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

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

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

1 person-years, respectively.

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

7 Convulsions: CBER analysis noted an imbalance in the
8 number of subjects (eight in the Shingrix and one in the
9 placebo group) reporting events by preferred term contained in
10 the narrow standardized MedDRA query of convulsions during the
11 30-day post-vaccination period. Available data were reviewed,
12 and two subjects had alternative etiologies for their
13 convulsions, and another two had a prior history of
14 convulsions. It is noted that some events were non-serious,
15 and as such, no narratives could be reviewed.

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

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

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

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

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

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

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

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

1 were 4 subjects out of 32, or 12.5%, who reported PHN in the
2 Shingrix group and 46 subjects out of 477, or 9.64%, who
3 reported PHN in the placebo group. Vaccine efficacy in terms
4 of reduction in PHN incidence in subjects with confirmed HZ was
5 0.29% with a lower bound of the 95% confidence interval below
6 zero.

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

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

21 That's it.

22 DR. EDWARDS: Thank you very much.

23 Are there questions?

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

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

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

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

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

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

1 blinding in the way that we did.

2 DR. OOSTVOGELS: Lidia Oostvogels from the clinical team.

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

11 DR. EDWARDS: Other questions? Yes.

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

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

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

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

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

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

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

13 DR. EDWARDS: Thank you.

14 DR. MILLER: Thank you.

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

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

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

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

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

4 (Pause.)

5 DR. AGGER: Oh, it's nice.

6 UNIDENTIFIED SPEAKER: All right.

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

8 (Pause.)

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

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

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

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

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

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

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

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

25 DR. STEGMANN: Um-hum.

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

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

8 DR. EDWARDS: Dr. Englund.

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

15 DR. AGGER: You're welcome.

16 DR. EDWARDS: Dr. Long.

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

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

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

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

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

13 DR. LONG: Canada.

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

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

22 DR. LONG: Thank you.

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

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

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

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

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

25 DR. EDWARDS: Dr. Sawyer.

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

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

14 It was a study where we used, as the control group, the
15 0, 2-month schedule. This is the group that has been bridged
16 to efficacy, and we looked at a 0, 6-month schedule compared to
17 0, 2-month and then a 0, 12-month. Each of those schedules had
18 two primary immunogenicity hypotheses. Both were matched for
19 the 0, 6-month schedule; only one was met for the 0, 12-month
20 schedule.

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

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

8 The second immunogenicity criterion that was utilized for
9 both studies was a GMC ratio with the 0, 2-month schedule. And
10 so that GMC ratio had a statistical criterion associated with
11 an upper limit that had to be less than 1.5. So what you see
12 for the 0, 6-month schedule is that the upper limit was 1.39,
13 so that confidence interval was met. And then for the 0,
14 12-month schedule, it was marginally exceeded, and therefore,
15 non-inferiority could not be declared for the 0, 12-month
16 schedule.

17 DR. EDWARDS: Dr. Janes.

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

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

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

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

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

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

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

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

1 cerebrovascular events, which illustrates that for both
2 categories, this is hemorrhagic cerebrovascular event and
3 ischemic cerebrovascular event, there is no difference.

4 However, as we are speaking about an aging population
5 where these kind of events do often occur, this is going to be
6 addressed in the pharmacovigilance plan as well as we are
7 looking into specifically for the targeted safety study as part
8 of the integral part of the pharmacovigilance plan, also
9 medically attended adverse events, which would enable us to
10 just follow up specific those events or the number of events
11 being reported in the postmarketing setting.

12 DR. EDWARDS: Dr. Sawyer.

13 DR. SAWYER: I have one more question about the
14 generalizability of the results across racial and ethnic
15 groups. I think you mentioned earlier that only three sites
16 were able to do the cell-mediated immune response. Where were
17 those sites, either geographically or can you characterize
18 those populations compared to the overall?

19 DR. MILLER: So the countries where those CMI analyses
20 were performed, there was one U.S. site, one site in the Czech
21 Republic, and one site in Japan.

22 DR. SAWYER: So I'm going to guess that they maybe had
23 even a lower percentage of Hispanic populations, for sure, if
24 not African American, than your overall; is that correct?

25 DR. MILLER: I don't have the specific numbers

1 specifically at hand, but certainly in the Japanese population,
2 for example, they were overwhelmingly Asian, and in Czech
3 Republic also, mostly European, and most likely at the U.S.
4 site, mostly Caucasian as well.

5 DR. EDWARDS: Dr. Kotloff.

6 DR. KOTLOFF: I apologize if you said this and I missed
7 it, but for some of the key adverse events that were observed
8 with possible imbalance, was there any difference between
9 Dose 1 and Dose 2? Because it seems like mostly what we're
10 looking at when it says less than 30 days, that could be within
11 30 days of either dose, but sometimes reactogenicity is seen in
12 association with one dose more than another. So I'm wondering
13 if there were any differential effects with any of these
14 adverse events of interest.

15 DR. AGGER: The way I looked at them was I just kind of
16 collated them and looked at them from time to onset from the
17 dose. I didn't look at Dose 1 and Dose 2. For example, for
18 optic ischemic neuropathy, there were only three events. For
19 convulsions, I looked after 30 days after any dose.

20 So I don't remember how I looked at gout, if there were
21 more after Dose 2 or Dose 1. Perhaps the Applicant can comment
22 on that? I only looked within the 30-day post-vaccination
23 period, after each dose. So I don't know whether there were
24 more after Dose 1 or Dose 2. Do you recall? No, I don't have
25 that on my number, sorry.

1 DR. EDWARDS: Dr. El Sahly.

2 DR. EL SAHLY: In the documents we received a week ago to
3 review in advance of the meeting, there was a mention of a
4 clinical trial where individuals received the HZ/su and they
5 all had to have had zoster at one point before. And in the
6 description of the data from that trial, there was mention of
7 an increased risk of zoster in -- I mean, the way I calculated
8 it, it ended up being 6 events in 90 individuals over a year,
9 but we didn't get any debriefing on it today and there wasn't
10 much more in the papers we received, so I wonder if having had
11 zoster is something, a precaution or something we need to be
12 concerned about.

13 DR. AGGER: Can you pull up backup Slide Number 3, please?
14 So you're speaking about Zoster-033. It was a non-IND study
15 conducted in two different countries. There were 96 subjects.
16 It was a one-armed study, and there were 96 subjects who
17 received two doses. There were six subjects, two of whom had
18 more than one episode of prior HZ, who reported nine events of
19 herpes zoster following vaccination during the 14 months; five
20 of them received antiviral medication.

21 Of the subjects, those who received two doses were vaccine
22 responders, so not clear why they would've experienced herpes
23 zoster. An informal analysis by our statistician calculated
24 the incidence at approximately 50 per 1,000 person-years, which
25 is higher than you would expect from unvaccinated people, not

1 after vaccination. You know, the data were somewhat confusing,
2 and the Sponsor has committed to performing a randomized
3 controlled study in this population to get more and more robust
4 information, and perhaps they'd like to speak about the plans
5 for that study.

6 DR. MILLER: Yeah, so Jacqueline Miller, Clinical R&D,
7 GSK.

8 As Dr. Agger mentioned, that study was limited by certain
9 methodological considerations, so it was a single-arm study,
10 unlike in the Phase III studies where there was a very rigorous
11 case definition defined by PCR, and in the case where PCR could
12 not be performed by the HZ/su, these were suspected cases that
13 were then reported by the investigator on the case report form.
14 So what we have about these cases are some clinical details,
15 which in some cases are difficult to interpret.

16 We also have accumulating information in the extension
17 studies that I mentioned in the Phase III study. So we have
18 continued our placebo subjects in an additional extension where
19 they are offered the HZ/su vaccine and they are followed, and
20 although they also are not undergoing the same diagnostic
21 procedures, we have 286 individuals who were actually herpes
22 zoster cases in the Phase III studies now enrolled in the trial
23 and received vaccination. Of those, we have one suspected
24 case. So we have some conflicting information, and so as
25 Dr. Agger mentioned, this is really why we believe it's

1 important to study this in a more rigorous way.

2 DR. EDWARDS: Dr. Long.

3 DR. LONG: Do you know if the zoster, was it the same site
4 of previous zoster, the same dermatome?

5 DR. MILLER: So maybe we can pull up the backup slide that
6 defines the cases. And maybe to address your question, we've
7 invited Dr. Myron Levin -- he was actually the chairman of our
8 HZAC, so he did a lot of these adjudications through the course
9 of the Phase III study, and he also looked at these Zoster-033
10 cases for us to help give us a more independent view on what
11 these cases might represent.

12 So thank you, Dr. Levin.

13 DR. LEVIN: Myron Levin, University of Colorado School of
14 Medicine and a paid consultant to GSK.

15 So I was able to look at all the data that was available
16 on these patients, and yes, there were some patients that had
17 recurrences in the same area; at least one person had it three
18 times in the same area. And there were certain features that I
19 looked at that I used to try to determine if this was a typical
20 case. They had to do with whether it was recurrent, whether it
21 was in the lumbar area, which is common for herpes simplex, how
22 quickly it healed, and how extensive it was. And a number of
23 the cases would not have made it, would not have been
24 considered a positive case by the adjudication committee.

25 So I think we were very limited in the amount of

1 information that we had of these cases. I actually requested
2 if we could get additional information, but all we eventually
3 had is what's presented here.

4 DR. EDWARDS: Was there any PCR data in any of these
5 patients?

6 DR. LEVIN: No, no.

7 DR. EDWARDS: Okay.

8 DR. LEVIN: No.

9 DR. EDWARDS: Yes, Holly.

10 DR. JANES: Following up on that, with regard to the
11 diagnoses of zoster in the efficacy trials where you did have
12 the PCR data, I noticed that there was an apparent imbalance in
13 both trials with regard to the fraction of the cases that were
14 definitively diagnosed based on the adjudication committee
15 versus based on PCR, suggesting perhaps that there were more
16 indeterminate PCR results in the vaccine versus placebo groups.

17 DR. AGGER: There were also a lot fewer cases.

18 DR. JANES: Right, a lot fewer cases. So was that -- do
19 you believe that that's a real trend? Does that have
20 implications for diagnosis of the breakthrough cases?

21 DR. MILLER: Well, so in the Zoster-006 trial, it's really
22 difficult to say because in the primary analysis there were
23 only six cases. But let me show you actually an overview of
24 the adjudication of our suspected cases just to give you the
25 full picture.

1 So in Zoster-006, and we'll discuss that first, there were
2 84 suspected cases in the HZ/su group, 340 in the placebo
3 group. Of those -- and here now, we're not talking about the
4 primary efficacy analysis, we're talking about that second
5 analysis that was performed at the very end of both of the
6 pooled studies. By that time there were nine cases. Of those,
7 7 were confirmed by PCR, 2 of them were confirmed by the HZAC,
8 and 75 of them were confirmed as not cases, and of those,
9 again, the majority were PCR confirmed versus HZAC confirmed.
10 If you then look at the placebo group, you have a much higher
11 proportion of cases that were confirmed as yes, so about 75%
12 overall. Of those, about 65% are PCR confirmed and 10% are
13 HZAC confirmed, and of those no, still, PCR is confirming the
14 majority of the cases. A similar pattern we're seeing in
15 Zoster-022, and you can see the data listed there.

16 DR. EDWARDS: Are there any other questions? Yes.

17 DR. LONG: You're looking reluctant to give me the
18 microphone. No, you're not reluctant.

19 DR. EDWARDS: If you have a question, please ask it.

20 DR. LONG: Okay. It's concerning the time frame of
21 looking especially for cerebrovascular events, vasculopathies,
22 etc., both in children with varicella and adults with strokes
23 following zoster vaccines, either of them. The risk was
24 increased through 6 months, so we don't know if it's -- I think
25 it's unlikely that the virus is still there. It could be the

1 inflammatory response or something that the inflammatory
2 response did early that makes one predisposed a little bit
3 later. So I don't think our usual rules of 30 days for
4 reactogenicity or adverse events, especially with live virus
5 vaccines or different kinds of kill virus vaccines, may apply
6 here, so I think the time frame is longer.

7 DR. AGGER: I think my SMQ analysis went from Month 0 to
8 Month 8, which would comprise 6 months after last vaccination.

9 DR. EDWARDS: So any other last questions? I'm happy to
10 have any more questions.

11 (No response.)

12 DR. EDWARDS: Okay. If not, then we've come to the period
13 for the Open Public Hearing. Before that occurs, I would like
14 to read about the Open Public Hearing.

15 Welcome to the Open Public Hearing. Please note that both
16 the FDA and the public believe in a transparent process for
17 information gathering and decision making. To ensure such
18 transparency at the Open Public Hearing session of the Advisory
19 Committee meeting, FDA believes it's important to understand
20 the context of an individual's presentation. For this reason,
21 FDA encourages you, the Open Public Hearing speaker, at the
22 beginning of your written or oral statement, to advise the
23 Committee of any financial relationship that you may have with
24 the sponsor, its product, and if known, its direct competitors.
25 For example, this financial information includes the sponsor's

1 payment of your travel, lodging, or other expenses in
2 connection with your attendance at the meeting. Likewise, FDA
3 encourages you, at the beginning of your statement, to advise
4 the Committee if you do not have such financial relationships.
5 If you choose not to address the issue of financial
6 relationships at the beginning of the statement, it will not,
7 however, preclude you from speaking.

8 Are there any speakers who will be talking today at the
9 Open Public Hearing?

10 Okay, Dr. Polanin.

11 DR. POLANIN: Thank you for the opportunity to speak
12 today. My name is Dr. Megan Polanin. I am a Senior Fellow at
13 the National Center for Health Research. Our research center
14 analyzes scientific and medical data and provides objective
15 health information to patients, providers, and policy makers.
16 We do not accept funding from industry, so I have no conflicts
17 of interest.

18 An effective shingles vaccine is important for public
19 health. As patients get older, they are more likely to develop
20 long-term pain or postherpetic neuralgia as a complication of
21 shingles. This pain can be severe and chronic. There is no
22 cure, and treatments do not reliably relieve pain for all
23 patients. The only way to reduce the risk of developing
24 shingles and PHN is to get vaccinated.

25 Like any public health strategy, a vaccine's benefits must

1 outweigh its risks. Based on available research, Shingrix has
2 displayed significant benefits compared with the current
3 shingles vaccine on the market. Shingrix showed much higher
4 levels of vaccine efficacy than the current shingles vaccine.

5 Zostavax only reduces the occurrence of shingles by about
6 half for patients 60 or older, and its effectiveness declines
7 as patients age. For patients 80 and older, Zostavax is only
8 18% effective.

9 Shingrix has displayed efficacy in preventing PHN in
10 patients 50 years and older by preventing shingles. Zostavax
11 is less effective in preventing PHN because it is less
12 effective at preventing shingles. For people who were
13 vaccinated and still developed shingles, Zostavax helped to
14 reduce the duration of PHN but not the severity of pain.
15 Shingrix can potentially be administered to vulnerable patients
16 with weakened immune systems. Zostavax is a live attenuated
17 vaccine and therefore is not safe for people with weakened
18 immune systems, such as patients who have had radiation or
19 chemotherapy and those with HIV.

20 Shingrix requires two doses while Zostavax is a one-time
21 injection; however, that is a small price to pay for a much
22 more effective vaccine.

23 Post-licensure studies are critical as we need long-term
24 data to evaluate Shingrix's long-term efficacy for patients 50
25 years and older. This is especially relevant since Zostavax

1 may no longer be effective 8 to 11 years after vaccination.
2 The company's proposed long-term follow-up studies will help to
3 determine whether Shingrix is able to protect older adults from
4 contracting shingles as they age. It is essential that those
5 studies be completed in a timely manner and that the company
6 provide adequate incentives to patients to stay in the study.

7 We do have some concerns about risks. Patients treated
8 with Shingrix had a higher rate of common adverse events such
9 as pain, swelling, and fatigue. In addition, one serious
10 adverse event, supraventricular tachycardia, was reported more
11 frequently for patients vaccinated with Shingrix compared with
12 patients who had not during a 30-day post-vaccination period.

13 We are also concerned about optic ischemic neuropathy,
14 which was reported within 30 days by two patients, within 2
15 months by another patient, and not reported at all in the
16 placebo group. These issues warrant further attention.

17 For that reason, we agree with the company and FDA
18 reviewers that continued pharmacovigilance is critical to
19 evaluate adverse events for patients vaccinated with Shingrix
20 compared to those vaccinated with Zostavax and those with
21 placebo. This should include uncommon adverse events observed
22 soon after vaccination and any other adverse events that may
23 arise with larger sample sizes and longer-term studies.

24 We concur with the FDA's request that the company
25 specifically address risks of inflammation from the vaccine,

1 which can lead to some of the adverse events reported during
2 pre-licensure studies.

3 We urge this Advisory Committee to recommend that the FDA
4 require critical post-approval long-term studies to further
5 evaluate the efficacy and safety of Shingrix. We also strongly
6 recommend that the company conduct subgroup analyses to ensure
7 that the vaccine is safe and effective for both women and men
8 and also people of color.

9 Thank you for the opportunity to share our perspective.

10 DR. EDWARDS: Thank you very much.

11 Okay, I think we now need to take some votes here and
12 discuss the questions first and then vote. So could we have
13 the first slide, the first question?

14 Are the available data adequate to support the efficacy of
15 Shingrix for the prevention of herpes zoster in adults 50 years
16 of age or older?

17 Let's go around the table and discuss this. Would you
18 like to start for us, Dr. Bok?

19 DR. BOK: I think this is very clear. It's a lot better
20 than the vaccine we have now. So the use of an adjuvant seems
21 to do the trick and especially now that population, the older
22 you get. So that's all.

23 DR. EDWARDS: Dr. Kotloff.

24 DR. KOTLOFF: I think that the data, there are very strong
25 data. My one concern about a gap is the small amount of data

1 in people of color and Hispanics, and I think further studies
2 would be very important in looking at those groups.

3 DR. EDWARDS: Dr. Lynfield.

4 DR. LYNFIELD: I agree.

5 DR. EDWARDS: Dr. Long.

6 DR. LONG: No concerns about efficacy.

7 DR. EDWARDS: Dr. Janes.

8 DR. JANES: No concerns about efficacy, albeit the
9 previous points being made about it being unclear about
10 efficacy in individuals with prior zoster.

11 DR. EDWARDS: Certainly, from my perspective, I think the
12 adjuvant markedly enhances the efficacy in ways that are really
13 quite impressive. The long-term duration and stability of the
14 CMI responses and the antibody, for as long as it's been looked
15 at, I think is also quite impressive.

16 Dr. Englund.

17 DR. ENGLUND: Yes, I'm very impressed by the efficacy, and
18 those of us who have worked with shingles really are -- I mean,
19 I am impressed, and I know that others would be impressed very
20 much with the efficacy. Thank you.

21 DR. EDWARDS: Dr. Wharton.

22 DR. WHARTON: Yeah, I agree with what others have said. I
23 think the data strongly support efficacy in the populations
24 that were studied. There still are some populations that were
25 not necessarily so well covered by the clinical trials, the

1 principal clinical trials that were presented, especially the
2 more diverse population that we see in the United States.

3 And there also is this question about people who
4 previously had zoster. I know that wasn't the primary target
5 of the principal studies, but there remained some unanswered
6 questions there.

7 DR. EDWARDS: Dr. El Sahly.

8 DR. EL SAHLY: The data presented do support the efficacy
9 within the constraint of the population selected, i.e., no
10 immune compromise, no previous zoster, etc., and for the
11 duration of 4 or 5 years.

12 DR. EDWARDS: Dr. Sawyer.

13 DR. SAWYER: I agree with my colleagues and including the
14 concerns about underrepresented populations.

15 DR. EDWARDS: Mr. Toubman.

16 MR. TOUBMAN: Agree. And I have a suggestion on that last
17 point, which is that it seems like -- that's why I asked the
18 question of Dr. Agger, if this is common that there's such low
19 incidence of Africans and African Americans in the studies.
20 One suggestion might be that the FDA could require that there
21 be a more representative percentage if you're going to -- when
22 you come before the Agency. I don't know if that's within our
23 purview or not, but I think it would be helpful.

24 DR. EDWARDS: Dr. Greenberg, would you like to comment?

25 DR. GREENBERG: Thank you, yeah. I agree with the others

1 around the table, and I think it's a major advance with regard
2 to the efficacy that we've seen today in the population with
3 some limitations, but clearly, a major advance.

4 DR. EDWARDS: Okay. So it looks, unless other people
5 would like to make any comments, that we're ready to vote,
6 then.

7 Just to read the question: Are the available data
8 adequate to support the efficacy of Shingrix for the prevention
9 of herpes zoster in adults 50 years of age and older?

10 Yes, no, or abstain.

11 If we can push the button now? It's blinking, so I think
12 we can.

13 (Committee vote.)

14 DR. EDWARDS: So it appears that we have 11 yeses and no
15 abstains and no noes. We will read the individuals that have
16 voted for or with yes.

17 Mr. Toubman, Dr. Sawyer, Dr. El Sahly, Dr. Wharton,
18 Dr. Englund, Dr. Edwards, Dr. Janes, Dr. Long, Dr. Lynfield,
19 Dr. Kotloff, and Dr. Bok.

20 Okay, so now we will put up the second question, and the
21 question is: Are the available data adequate to support the
22 safety of Shingrix when administered to adults 50 years of age
23 and older?

24 Let's start on this end this time.

25 Dr. Greenberg.

1 DR. GREENBERG: My interpretation of the data are that the
2 recognized increases in solicited injection site and systemic
3 reactions are what they are, and they're short-lived and
4 generally reasonable. And it's a risk-benefit analysis in my
5 view, so an increase in short-term reactions in that risk-
6 benefit analysis are fine, in my opinion.

7 And then some of the other more fine points around some of
8 the events that were occurring, I think those are subjects of
9 long-term pharmacovigilance, and I'm sure those can be
10 evaluated over time.

11 DR. EDWARDS: Mr. Toubman.

12 MR. TOUBMAN: I agree with what was just said. I don't
13 know that the pharmacovigilance program, how rigorous it is,
14 but it certainly seems that all of the issues that were
15 identified warrant very careful review.

16 DR. EDWARDS: Dr. Sawyer.

17 DR. SAWYER: Yes, I agree with Dr. Greenberg's summary.
18 The adverse event profile is very well clarified for us, and we
19 know it going in, and so I think the ongoing studies will
20 illuminate the rarer event.

21 DR. EDWARDS: Dr. El Sahly.

22 DR. EL SAHLY: I agree about -- with what Dr. Greenberg
23 just said.

24 DR. EDWARDS: Dr. Wharton.

25 DR. WHARTON: Yeah, I agree with the statements that have

1 been already. I would like to comment on, it is great seeing
2 clinical studies that include so many people who are in the age
3 range that were included in these studies where comorbidities
4 are so common, and underlying medical conditions and events
5 which probably are unrelated to vaccination are inevitably
6 going to occur during follow-up periods and require careful
7 evaluation to make sure that we're not seeing important
8 imbalances that actually reflect vaccine safety issues.

9 I think there's been a really thoughtful job done by both
10 the Sponsor as well as by CBER in looking at a large amount of
11 very complicated adverse event data, and I don't see anything
12 in it that provides a high level of concern. But clearly it is
13 going to be important going forward, and there will be many
14 events that occur post-vaccination that will have to be
15 evaluated in the context of post-licensure surveillance to
16 evaluate, to make sure that we understand the safety profile.

17 DR. EDWARDS: Dr. Englund.

18 DR. ENGLUND: I agree. I think doing vaccine trials in
19 high-risk people, which this is, and which ongoing trials which
20 we all are very excited about will be -- are very challenging,
21 they're very challenging. And I think when we do enough
22 comparative analysis of about 1,000 different data points, the
23 fact that we found some significant factors -- they weren't
24 even significant -- but some imbalances is to be expected, and
25 I think that's very important.

1 I also would echo the comment that Dr. Sawyer made. This
2 is good, patients need to know going into this, that there is a
3 chance of some short-lived reactions. We know that they need
4 to be advised of that by their care provider. But I believe
5 the answer to Question 2 is yes.

6 DR. EDWARDS: Certainly, I applaud the comprehensive
7 analysis of all of these safety signals, and as Melinda said, I
8 think that both the Sponsor and FDA have done a really
9 wonderful job of really digging down and trying to answer the
10 questions.

11 And I also think it is reassuring that 006 and 022 sort of
12 had -- some of the adverse events were reversed in the vaccine
13 and the control groups in the two studies and making me think
14 that maybe it's the gremlins of randomization and not really
15 the gremlins of adverse events. So, certainly, we need to have
16 post-licensure surveillance as has been outlined, but I think
17 that the plan for post seems very adequate.

18 Dr. Janes.

19 DR. JANES: Yeah, I'm in full agreement with the prior
20 comments. Nothing further to add.

21 DR. EDWARDS: Dr. Long.

22 DR. LONG: Well, I think I've been a little bit swayed by
23 listening to starting on the other side of the room because I
24 think this is a very good case for the first licensure of this
25 adjuvant in the United States because the efficacy seems pretty

1 compelling, the disease is morbid, and there are a lot of
2 people whose lives can be changed. But it is inducing the host
3 to make an inflammatory response that they otherwise wouldn't
4 be making. So it is different, it is unusual, and I wish there
5 were more safety data in the United States with the kind of
6 risk people that we have for some of the concerns that there
7 are regarding safety.

8 So I think it is, with the data that we have at hand, do
9 we have enough information that the potential benefits outweigh
10 the concerns of risk? And I'm going to maybe decide that as we
11 finish the table.

12 DR. EDWARDS: Dr. Lynfield.

13 DR. LYNFIELD: I agree with, I think, the comments that
14 people have made. I think that it is a difficult thing to do
15 to study people in this age group. It is a very morbid
16 disease, and I think that we do have data that show that it is
17 safe. I think it makes sense to have a pharmacovigilance plan
18 going forward for all the reasons everyone has already
19 articulated. We need to really ensure that the safety is
20 there, we need to look at additional populations, and I am
21 comfortable with the plan that's in place.

22 DR. EDWARDS: Dr. Kotloff.

23 DR. KOTLOFF: Yes, thanks. So I would like to echo the
24 congratulations to the company and to CBER on taking this huge
25 body of data and analyzing it and presenting it so clearly.

1 I think that the future, part of the future of vaccines is
2 that we're going to see more powerful adjuvants and that we're
3 going to be vaccinating more vulnerable populations, and so
4 there may be new reactogenicity that we don't understand that
5 we're going to have to very carefully look at. So I think that
6 the -- you know, I just want to emphasize the importance of a
7 very carefully thought out pharmacovigilance plan.

8 And particularly with regard to SVT, I'm not a
9 cardiologist, but there may be differences in the ability of an
10 adjuvant to trigger atrial fib and SVT, and so I think that
11 that also has to be carefully looked at so we don't dilute a
12 signal by lumping it together with potentially unrelated
13 factors.

14 DR. EDWARDS: Dr. Bok.

15 DR. BOK: Yes, I believe the answer is yes. I am going to
16 join on the congratulations. I think it's a great study,
17 especially on immunosenescence and immunosenescent populations.
18 For me, the safety profile is strong, and it's either strong or
19 it's going to be addressed with the pharmacovigilance plan.

20 The only question I have is following up. I was also
21 confused by the 033, which is a little bit -- the results are
22 not clear, and it would be nice to see, once the herpes zoster
23 cases are confirmed, to see those people vaccinated and follow
24 the safety profile and especially keeping in mind how long
25 after the episode you're going to vaccinate them and what's the

1 safety after that. So, for me, that's the only thing I would
2 like to just comment on.

3 DR. EDWARDS: Okay, thank -- Dr. Greenberg.

4 DR. GREENBERG: Sorry, I just wanted to get back to a
5 comment that was made a couple times today. My background,
6 like yours and many, are in pediatric infectious diseases, so
7 that's where I did most of my clinical trials prior to
8 industry, where, you know, you pretty much put your study
9 investigators in areas in the country and in populations where
10 there are diverse individuals and you'll get a diverse study
11 population. It is different in seniors. For a variety of
12 social and other reasons, they tend not to participate in these
13 types of trials or in vaccine trials in general. It is a big
14 challenge. I don't have a solution, and I don't question that
15 we should question, you know, how to get that done and have a
16 more diverse population in our senior trials, but it's not
17 easy. It's not just a matter of choosing investigators in the
18 right places.

19 DR. EDWARDS: Thank you. Well said.

20 Okay, any other comments?

21 (No response.)

22 DR. EDWARDS: Okay. So the question is: Are the
23 available data adequate to support the safety of Shingrix when
24 administered to adults 50 years of age and older?

25 So vote yes, no, or abstain.

1 (Committee vote.)

2 CAPT HUNTER-THOMAS: Okay, so the total is 11 yes, zero
3 abstain, and zero no.

4 And we will read the names individually for the record
5 starting with Dr. Bok, yes; Dr. Kotloff, yes; Dr. Lynfield,
6 yes; Dr. Long, yes; Dr. Janes, yes; Dr. Edwards, yes;
7 Dr. Englund, yes; Dr. Wharton, yes; Dr. El Sahly, yes;
8 Dr. Sawyer, yes; Dr. Toubman, yes.

9 Thank you.

10 DR. EDWARDS: Are there any other comments that FDA would
11 like to make?

12 DR. GRUBER: Let me confer real quick with my colleagues
13 here, just a little glance back. Yes, I was confirmed that we
14 are all good, and I really want to thank the Committee for the
15 deliberations; it was really helpful. And yeah, that's all, I
16 think. We're going to continue working with the Applicant on
17 this file.

18 DR. EDWARDS: Thank you, thank you.

19 Did you have a comment, Mr. Toubman?

20 MR. TOUBMAN: Yes, I did actually have a question, which
21 is that in the situation where it's been discussed where for
22 people who have already had the disease, zoster, there's a
23 study that's -- it's unclear, you know. Is this a thing -- is
24 this a situation where FDA, in the approval, in the license,
25 makes a comment about that, or how does that work in terms of

1 educating clinicians that there's an issue there?

2 DR. GRUBER: So we have actually means of describing a
3 certain data or lack thereof in the package insert, so I think
4 we're going to be discussing how we're going to be describing
5 this. So you were referring to those people that had previous
6 herpes zoster and, you know, what happens to them if they're
7 going to be vaccinated with Shingrix. Yeah, I mean, as you
8 heard, the Applicant is going to do a study, you know, to look
9 into this further, so right now I can envision the package
10 insert that there are no data on this at this time. But,
11 again, this is something that we're still going to be
12 discussing on how we include or not include such information or
13 data in the package insert.

14 DR. EDWARDS: Thank you.

15 And thank you, members of the Committee. Thank you,
16 members for the audience, those on the webcast, and certainly
17 thank you to the Applicant for an excellent presentation.

18 (Whereupon, at 2:14 p.m., the meeting was concluded.)

19

20

21

22

23

24

25

1 C E R T I F I C A T E

2 This is to certify that the attached proceedings in the
3 matter of:

4 148TH MEETING OF THE VACCINES AND RELATED BIOLOGICAL PRODUCTS

5 ADVISORY COMMITTEE

6 September 13, 2017

7 Silver Spring, Maryland

8 were held as herein appears, and that this is the original
9 transcription thereof for the files of the Food and Drug
10 Administration, Center for Biologics Evaluation and Research.

11

12

13

14

15

16 TOM BOWMAN

17

Court Reporter

18

19

20

21

22

23

24

25

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947