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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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147TH MEETING OF THE VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

+ + +

July 28, 2017
8:30 a.m.

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

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KAREN KOTLOFF, M.D.	Voting Member
OFER LEVY, M.D., Ph.D.	Voting Member
RUTH LYNFIELD, M.D.	Voting Member
PAMELA McINNES, D.D.S., M.Sc. (Dent)	Voting Member
ARNOLD MONTO, M.D.	Voting Member
MARK SAWYER, M.D.	Voting Member
MELINDA WHARTON, M.D., M.P.H.	Voting Member
JACK BENNINK, Ph.D.	Temporary Voting Member
MARIE R. GRIFFIN, M.D., M.P.H.	Temporary Voting Member
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MEI-LING TING LEE, Ph.D.	Temporary Voting Member
MILTON PACKER, M.D.	Temporary Voting Member
JOHN W. WARD, M.D.	Temporary Voting Member
JAY M. PORTNOY, M.D.	Acting Consumer Representative
HENDRIK NOLTE, M.D., Ph.D.	Acting Industry Representative

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M E E T I N G

(8:35 a.m.)

DR. EDWARDS: My name is Dr. Kathy Edwards. I'm from Vanderbilt University. I'm the VRBPAC Chair, and I'd like to welcome you all this morning, the members, the participants, the public, and the audience viewing on the webcast.

To begin, I would like to start with having the people on the Panel introduce themselves, where they're from, and what their expertise is.

So, Dr. Nolte, would you like to begin, please?

DR. NOLTE: Yeah, my name is Hendrik Nolte. I'm Senior VP of Research and Development for ALK. My expertise is immunology and allergy, and I am a respiratory physician also.

DR. WARD: Good morning. I want to recognize that this is World Hepatitis Day around the world, and I'm Dr. John Ward. I'm Director of the Division of Viral Hepatitis at CDC in Atlanta.

DR. HOOFNAGLE: My name is Jay Hoofnagle. I'm the Director of the Liver Disease Research Branch at NIDDK and a former member of the FDA. I was actually, many years ago, Acting Director of the Hepatitis Branch when things were simpler.

(Laughter.)

DR. BENNINK: My name is Jack Bennick. I'm with NIH/NIAID. I am a viral immunologist.

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

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

DR. MONTO: Good morning. I'm Arnold Monto, Professor of Epidemiology at the University of Michigan School of Public Health, and I do infectious disease trials.

DR. WHARTON: I'm Melinda Wharton. I'm Director of the Immunization Services Division of the Centers for Disease Control and Prevention.

DR. GRIFFIN: I'm Marie Griffin. I am a Professor of Health Policy and Medicine at Vanderbilt. I'm a pharmacoepidemiologist.

DR. EDWARDS: I'm Kathy Edwards, Professor of Pediatrics at Vanderbilt, a vaccinologist and of pediatric infectious disease.

DR. SAWYER: I'm Mark Sawyer. I am a Professor of Pediatric Infectious Disease at the University of California, San Diego.

DR. KOTLOFF: I'm Karen Kotloff. I am a Professor of Pediatric Infectious Disease at the University of Maryland, and I do research in vaccinology and epidemiology.

DR. LEVY: Hi, I'm Ofer Levy. I am a physician/scientist

at Boston Children's Hospital and Harvard Medical School. I direct the Precision Vaccines Program at Boston Children's, directed at developing novel vaccine formulations for special populations.

DR. McINNES: Good morning. I'm Pamela McInnes. I am Deputy Director of the National Center for Advancing Translational Sciences, the newest NIH institute.

DR. PACKER: I'm Milton Packer from Baylor University Medical Center in Dallas. I am a cardiovascular clinical trialist/cardiologist. I'm on loan from the Division of Cardiac and Renal Drug Products where I'm a member. I think they sent me out for a player to be named in the future.

DR. LEE: Good morning, my name is Mei-Ling Ting Lee. I am a Professor of Biostatistics at the University of Maryland.

DR. GRUBER: Hello, good morning. Marion Gruber. I'm the Director of the Office of Vaccines Research and Review at CBER.

DR. SUN: Good morning, my name is Wellington Sun. I'm the Director of the Division of Vaccines & Related Product Applications within the Office of Vaccines at CBER.

DR. EDWARDS: Thank you very much.

We'd now like to have administrative announcements or conflict of interest statements from Serena Hunter-Thomas.

CAPT HUNTER-THOMAS: Good morning, everyone. My name is Captain Serena Hunter-Thomas, and on behalf of the FDA and the Center of Biologics Evaluation and Research and VRBPAC, we

would like to welcome you all today to this meeting. Dr. Edwards is your Chair for this meeting.

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

CDER -- CBER, excuse me, has a press media representative. Mr. Richards, are you here? His name is Paul Richards, and he's in the far back today. Thank you.

And our transcriptionist for the meeting today is from Free State, and his name is Mr. Dominico Quattrociocchi?

COURT REPORTER: Close enough.

CAPT HUNTER-THOMAS: Close enough. Thank you.

When you make your comments today, or ask any questions, please speak up so that all your statements can be recorded.

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

When speaking, please press the microphones to talk, and when you're done, switch them off when you're finished. Please make sure that you speak clearly and loudly into the microphone as the transcriptionist will -- and members of the public and those listening via webcast need to hear this discussion.

Staff is working on your behalf, VRBPAC members and Committee members, to arrange for lunch, and during the break this morning, if you need to make alternate arrangements, you

can do so with either Rosanna or Denise at the kiosk.

I would like to now proceed to reading the Conflict of Interest Statement for this meeting for the public record.

The Food and Drug Administration is convening today, July 28th, 2017, for the 147th meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. This meeting is determined to be a particular matter involving specific parties.

At this meeting, in the open session, the Committee will discuss and make recommendations on the safety and efficacy of a hepatitis B vaccine manufactured by Dynavax.

The following information on the status of this Advisory Committee's compliance with federal ethics and conflict of interest laws, including, but not limited to, 18 U.S. Code 208, is being provided to participants at this meeting and to the public. This Conflict of Interest Statement will be available for public viewing at the registration table.

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

Related to the discussions at this meeting, all members and consultants of this Committee have been screened for

potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouse or minor children and, for the purpose of 18 U.S. Code 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts and grants/CRADAs; teaching/speaking/writing; patents and royalties and primary employment.

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

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

Dr. Hendrik Nolte is currently serving as the alternative Industry Representative for this meeting. Dr. Nolte is employed by ALK, Incorporated. Industry representatives act on behalf of all related industry and bring general industry perspective to the Committee. Industry representatives are not special government employees. They do not vote, and they do not participate in the closed session.

Dr. Jay Portnoy is serving as an acting Consumer Representative for this meeting, and he is joining us by phone today. Consumer representatives are special government employees and therefore are screened for their financial conflicts of interest and are cleared prior to their participation.

At this meeting there may be regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflicts of interest.

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

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

This concludes my reading of the Conflict of Interest

Statement for the public record, and I now would like to hand the meeting back over to our Chair, Dr. Kathryn Edwards.

Thank you.

DR. EDWARDS: Thank you, Captain Hunter-Thomas.

I would like to now introduce the first speaker, Dr. Marian Major, Chief of the Laboratory of Hepatitis Viruses in the Division of Viral Products of the Office of Vaccines Research and Review. Thank you.

DR. MAJOR: Thank you very much. And good morning, everyone. Welcome to the Vaccines and Related Biological Products Advisory Committee meeting.

My name is Marian Major. I'm Chief of the Laboratory of Hepatitis Viruses in the Division of Viral Products, and I'd like to extend a welcome to our distinguished members of our VRBPAC panel and --

DR. EDWARDS: Could you move a little closer to the microphone? It's a little hard to hear you.

DR. MAJOR: -- particularly to the subject matter experts. Thank you all very much for being here today.

Okay, so today we are going to discuss Heplisav-B. This is an adjuvanted hepatitis B vaccine from Dynavax Technologies. It contains hepatitis B surface antigen combined with CpG 1018 adjuvant.

I'd like to start by just giving some background on the currently licensed hepatitis B vaccines that are in the United

States. These are both approved for immunization against infection caused by all known subtypes of hepatitis B virus.

We have Engerix-B, which is manufactured by GlaxoSmithKline. It was licensed in 1989. It consists of recombinant HBV surface antigen produced from yeast cells, and it is absorbed onto aluminum hydroxide.

We also have Recombivax HB, which is manufactured by Merck. This was licensed in 1986. It also consists of recombinant HBV surface antigen produced from yeast cells, and it's absorbed onto aluminum hydroxyphosphate sulfate.

This shows the dosage and administration for these two vaccines. Both vaccines are administered through intramuscular inoculation.

Engerix-B, for people from birth through 19 years of age, receive 10 µg of hepatitis B surface antigen three times at 0, 1, and 6 months. For people 20 years of age and older, they receive 20 µg of surface antigen at 0, 1, and 6 months. And adults on hemodialysis receive 40 µg of surface antigen at 0, 1, 2, and 6 months.

Recombivax HB, a very similar administration schedule: For people from birth through 19 years of age, they receive 5 µg of surface antigen 0, 1, and 6 months. People 20 years of age and older receive 10 µg of surface antigen at each of the three time points. And adults on hemodialysis receive 40 µg of surface antigen also at 0, 1, and 6 months.

Now, there are also some currently licensed combination hepatitis B vaccines. These are both manufactured by GlaxoSmithKline. We have Twinrix, which is indicated for protection against hepatitis B and hepatitis A for people 18 and older; and Pediarix, which is indicated for protection against diphtheria, tetanus, pertussis, hepatitis B, and polio, for children 6 weeks through 6 years. And the hepatitis B component in these two vaccines is the same as that contained in the monovalent Engerix-B.

So there are a couple of alternate adult dosing schedules, again, through intramuscular administration, and these might be used for specific populations such as people who have or might have been recently exposed to the virus or for travelers to high-risk areas.

So the Engerix-B, people would receive 20 µg of hepatitis B surface antigen at 0, 1, and 2 months with a boost at 12 months; and Twinrix, adults would receive 20 µg of surface antigen at 0, 7, and 21 to 30 days with a boost at 12 months.

So I'd now like to move on to talking about Heplisav-B, which is the vaccine we'll be discussing today.

This also, like the currently licensed vaccines, consists of recombinant hepatitis B surface antigen produced from yeast cells. It's combined with CpG 1018 adjuvant, which is a cytosine phosphoguanosine oligodeoxynucleotide, or CpG ODN. This adjuvant is not contained in any currently licensed U.S.

vaccines.

And the vaccine is indicated for immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older. And the dosage consists of two doses, 20 µg of hepatitis B surface antigen combined with 3,000 µg of the CpG 1018 adjuvant, and this is given at a 0- and 1-month schedule.

So what are CpG ODNs? These are synthetic DNA molecules, oligodeoxynucleotides, or ODNs, with phosphorothioate backbone containing unmethylated cytosine phosphoguanosine, or CpG, motifs. Now, the CpG motifs occur at a higher frequency in bacterial and viral DNA than vertebrate DNA, and CpG ODNs have different immune enhancement effects in different species. The CpG ODN adjuvants, in general, have been found to trigger B cell activation and preferentially induce a Th1-like over a Th2-like CD4 T helper immune response.

And this is a very high overview of the difference between Th1 and Th2 responses. Th1 responses are generally characterized by the production of proinflammatory cytokines, such as interferon-gamma and TNF-alpha, and this leads to cell-mediated immunity and an IgG2a isotype antibody response, whereas Th2 responses are characterized by interleukin-4 production as well as several other cytokines and leads to a humoral immune response dominated by IgG1 and IgE antibodies.

CpG mode of action is that CpG ODNs are toll-like receptor

agonists, or TLR, and TLRs are proteins on innate first-responder immune cells, such as monocytes and dendritic cells, that recognize molecules from invading microbes. TLRs recognize molecules that are shared by many different microbes, but these are distinguishable from host molecules. The CpG ODNs function via a very specific TLR, TLR9, and TLR9 is expressed mainly on plasmacytoid dendritic cells and memory B cells.

So the CpG 1018 adjuvant proposed mode of action is that it stimulates TLR9 in the plasmacytoid dendritic cells that are taken up by hepatitis B surface antigen. It converts those plasmacytoid dendritic cells into activated dendritic cells and present surface antigen epitopes to the immune system, and it promotes differentiation of the CD4 cells that then leads to antibody secretion by HBsAg-specific B cells.

So I'd now like to talk a little bit about the use of anti-HBs antibody to predict protection. So early hepatitis B vaccine trials used the prevention of HBV infection as the clinical endpoint. The data from those early HBV vaccine studies, which actually used Heptavax, a plasma-derived hepatitis B surface antigen vaccine no longer on the market, showed antibody levels to the surface antigen of greater than 10 mIU/mL, and this correlated with protection.

So post-vaccination and anti-HBs level of greater than or equal to 10 mIU/mL is accepted as conferring protection. And

this type of correlate of protection can be used as an indicator of clinical effectiveness in a traditional route to licensure.

So what do we know about the levels of anti-HBs and protection? So it's accepted that higher anti-HBs levels, post-vaccination, have been associated with greater persistence of antibody in vaccinees. However, decreased titers to less than 10 mIU/mL or even complete disappearance of anti-HBs does not necessarily mean a loss of protection. Immunological memory is maintained in vaccinees despite declines in anti-HBs levels. So although anti-HBs may become undetectable in a substantial proportion of vaccine responders, breakthrough infections are rare and mainly asymptomatic.

So the duration of protection: This has been looked at extensively in data from prolonged follow-up studies using the original plasma-derived hepatitis B vaccine, and in these studies, over 94% of primary responders had evidence of continued protection after 30 years and no chronic infections were documented in the vaccine recipients.

So for recombinant hepatitis B surface antigen vaccines, we don't have data as long as 30 years, but studies have also shown that these confer long-term protection and persistent immunological memory for at least 18 years.

So moving on to the Heplisav-B clinical studies: Seroprotection rate in these studies, or SPR, was used as the

endpoint to support effectiveness, and you'll see that discussed today. And SPR is defined as the proportion of individuals achieving an anti-HBs concentration of greater than or equal to 10 mIU/mL after vaccination.

All the Phase 3 trials performed by Dynavax compared antibody responses following injection with either two doses of Heplisav-B or three doses of Engerix-B.

I'll just give a little bit of background on the regulatory history of Heplisav-B. The initial BLA was submitted in April 2012. This included data from two Phase 3 trials (DV2-HBV-10 and DV2-HBV-16), and you'll hear about those today.

A VRBPAC meeting was held in November 2012 to discuss the immunogenicity and safety of the vaccine in adults 18 through 70 years of age, and the committee members voted 13 to 1 that the immunogenicity data were adequate to support effectiveness. The committee members also voted 5 to 8 with 1 abstention that the available data were adequate to support safety. And it was noted that in view of the novel adjuvant, members recommended a larger pre-licensure safety database.

As a result of this VRBPAC, the Applicant conducted an additional Phase 3 safety and immunogenicity study (DV2-HBV-23), which you'll also hear about today. Now, CBER considers that effectiveness was established in the two previous Phase 3 studies; therefore, this VRBPAC discussion will focus on the

safety of Heplisav-B.

As a result, these are the questions that we have to the Committee:

Do the available data support the safety of Heplisav-B when administered to adults 18 years and older? Please vote yes or no.

And if yes, please comment on the proposed pharmacovigilance plan. If no, do the presented data support usage in a more specific subpopulation? Please vote yes or no.

Also, what additional studies (pre- and post-licensure) are needed to further evaluate the safety of Heplisav-B in the general adult population and/or in specific subpopulations?

Thank you.

DR. EDWARDS: Thank you very much. Are there questions for Dr. Major?

(No response.)

DR. EDWARDS: Thank you very much.

We will now begin the Sponsor presentations from Dynavax. I would like to introduce the first speaker, Dr. Robert Janssen, the CMO and Vice President of Clinical Development from Dynavax.

Dr. Janssen.

DR. JANSSEN: Good morning. I'm Rob Janssen, the Chief Medical Officer at Dynavax Technologies Corporation. We're very pleased to be here today to present our data on

Heplisav-B, a candidate vaccine for immunization against hepatitis B virus infection in adults.

In our presentation today, you'll hear that Heplisav-B fills an important need in adults by providing significantly higher and earlier seroprotection against hepatitis B compared with existing vaccines, using fewer doses and with an acceptable safety profile.

Like the currently approved hepatitis B vaccines, Heplisav contains a yeast-derived recombinant hepatitis B surface antigen. The surface antigen in Heplisav is produced in *Hansenula polymorpha*. Over a billion doses of this antigen have been administered worldwide.

So the major difference is in the adjuvant. Heplisav uses a toll-like receptor 9 agonist. We call it 1018. The current licensed vaccines use aluminum salt.

Heplisav is a sterile liquid dosage form. It comes in half mL dose vials, and it contains 20 µg of surface antigen and 3 mg of 1018. It's administered in a two-dose series 1 month apart by intramuscular injection compared with the three-dose series over 6 months for the currently approved vaccines.

We presented Heplisav previously to VRBPAC in 2012. Based on statistically significantly higher seroprotection rates, the Committee voted 13 to 1 that the immunogenicity data supported the effectiveness of Heplisav for the prevention of hepatitis B

virus infection in adults.

However, in a 5 to 8 vote with 1 abstention, the majority of the committee members considered the size of the pre-licensure safety database of 4,400 subjects who received Heplisav and 1,400 subjects who received Engerix as insufficient to support the safety of Heplisav.

In addition, committee members expressed concern regarding a potential imbalance in immune-mediated events, as well as the relative lack of racial minority populations from the U.S. in the safety database.

In 2014 Dynavax launched a new study that we call HBV-23 that successfully addressed the issues previously raised by VRBPAC and FDA. HBV-23 doubled the size of the safety database, improving the ability to detect an imbalance in infrequent serious autoimmune events. The study was conducted in a diverse population in the United States. The design of this study was developed in consultation with FDA.

The proposed indication for Heplisav is for active immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.

Now, let me provide you an overview of our clinical program that supports this BLA.

Our full clinical development program includes three pivotal trials, they're shown in dark blue, and a supportive trial, shown in light blue. These trials enrolled more than

14,000 adult participants. The focus of our presentation today will primarily be on data from our three pivotal trials. Individual data, key individual safety data from individual studies were presented in the briefing book.

Now, for our agenda today, Dr. William Schaffner will discuss the unmet public health need for hepatitis B vaccination in adults. Then Dr. Stanley Plotkin will discuss the adjuvant 1018. I'll review the immunogenicity and safety for Heplisav, and Dr. Darren McGuire will provide his assessment of the cardiovascular safety. I'll then return to the lectern to discuss our proposed postmarketing plan. And lastly, Dr. Greg Poland will provide his clinical and public health perspective on the benefit-risk profile.

All external experts have been compensated for their time and travel but have no financial interest in Dynavax.

Now, we also have additional external experts as well as an expert from Dynavax with us here today to help answer your questions.

Thank you. And I'll now turn the lectern over to Dr. Schaffner.

DR. EDWARDS: Yes. Yes, Dr. Levy would like to ask a question of you, Rob.

DR. LEVY: I just had a quick question. I don't know if you're the right one to answer or one of the subsequent speakers. I understand the vaccine, Heplisav, is composed of

hepatitis B antigen and the CpG adjuvant. I had a question in terms of the formulation. How are these combined? Is there any covalent attachment or just co-added in solution?

DR. JANSSEN: They're just co-added; it's a mixture.

DR. LEVY: Okay.

DR. EDWARDS: Thank you.

Dr. Schaffner, the Unmet Public Health Need.

DR. SCHAFFNER: Thank you, Dr. Edwards. Good morning. I'm Bill Schaffner, Professor of Preventive Medicine and Infectious Diseases at the Vanderbilt University School of Medicine. I'm here today on World Hepatitis Day to discuss the public health need for an improved hepatitis B vaccine that overcomes the limitations of the currently licensed vaccines.

Hepatitis B transmission remains a problem with more than 20,000 new infections each year and a 21% increase from 2014 to 2015; 95% of these new infections occur in adults.

Chronic hepatitis B infection can be devastating. Approximately two million individuals are currently living with chronic hepatitis B, which can result in cirrhosis and liver cancer. Roughly 5,000 Americans each year still die from complications of hepatitis B, and hepatitis B is the most common viral cause of fulminant hepatic failure. Cirrhosis or scarring of the liver can cause illness, repeat hospitalizations, end-stage liver disease for years before culminating in death or liver transplantation. Hepatocellular

carcinoma is often diagnosed late, and it's commonly fatal.

With this disease burden as a backdrop, in 1991 the Advisory Committee on Immunization Practices, the ACIP, recommended routine vaccinations for infants, catch-up vaccinations in adolescents, and reiterated the need for vaccination of adults with risk factors for infection. These risk factors include sexual exposure, particularly among heterosexuals with multiple sex partners, men who have sex with men, and persons with parenteral exposure, especially among injection drug users. Healthcare providers, which is many of us, exposed to body fluids and sharps also should be vaccinated.

More recently, in 2011, the ACIP recommended that all patients with diabetes less than 60 years of age be vaccinated against hepatitis B just as soon as possible after their diagnosis of diabetes, and those persons with diabetes 60 years of age and older be vaccinated at the discretion of their physician.

Indeed, persons with diabetes have an increased risk of acquiring hepatitis B infection, and those with acute hepatitis B have a case fatality rate of approximately two and a half times higher than people without diabetes. Further, patients with diabetes are twice as likely to develop the long-term complications of hepatitis B.

In the United States there are about 23 million adults

with diabetes, and another 1½ million new cases are diagnosed each year. Importantly, they have a mean age of their diagnosis of 54 years, which likely means they were not immunized as children and are now at an age where they do not respond optimally to current vaccines.

Recently, the National Academies have called for eliminating viral hepatitis as a public health problem in the United States. In the CDC's 2017-2020 action plan, Goal 1 is to prevent new viral hepatitis infections.

So with all of these recommendations and calls to action, how are we doing? This slide shows rates of reported cases of acute hepatitis B by age in the United States over the past 10 years. It's not adjusted for the known underreporting, which can underestimate new infections by five to tenfold.

In the pediatric population, look at the bottom of the slide. Shown here in green we have had tremendous success in virtually eliminating hepatitis B with effective vaccines and a robust vaccination program. We also see a steady decrease in hepatitis B in young adults age 20 to 29 years as those protected children are gradually aging up. However, when we look at older populations, age 30 to 39, 40 to 49, and 50 to 59 years, we're out of the reach of immunization programs, and where the current vaccines are less effective, we're seeing stable if not increasing rates, and there, ladies and gentlemen, is the public health need.

Finally, even in those 60-plus years, where the historical incidence has been lower, even here we're seeing stable if not increasing rates. Again, these adult populations do not respond optimally to the current vaccines. Bottom line: What we're doing is not working optimally in adults. The question is why?

So hepatitis B infections are still occurring. The highest incidence rates are seen in 30- to 45-year-old men, in people with diabetes, and in people of black race.

We're seeing striking increases in hepatitis B in certain populations. Recently, for example, the CDC reported a 114% increase in acute hepatitis B in three states, Kentucky, West Virginia, and in my own state of Tennessee, likely due to injection drug use associated with the ongoing opioid epidemic. Indeed, recent data show that the largest age group of people in New York City seeking treatment for opioid dependence has increased to those aged 50 to 59 years.

So here are the most recent data published earlier this year, reporting coverage rates for three-dose hepatitis B vaccination in at-risk adults. The bars represent adults vaccinated with all three doses. Among populations at risk, vaccination rates are low, such as 34% in the total high-risk population and only 24% in adults with diabetes. Even in healthcare providers with direct patient care responsibilities, the rate is only 74%, whereas the Healthy People 2020 goal is

90%.

Let me now point out some of the limitations to the current vaccines when used in adults.

In adults, unlike in children, currently licensed vaccines have several limitations, including reduced seroprotection, reduced adherence to the 3-dose/6-month regimen, as well as prolonged time to seroprotection of at least 6 months. Let me provide more details on all three.

With regard to the first limitation, compared to the use in children, the current vaccines have been shown to provide lower seroprotection in adults, with particular challenges in men, older persons, persons with diabetes, obese persons, and persons who smoke.

Additionally, we know that adherence to the third dose at 6 months is essential for most adults to be fully protected, but this is challenging to complete. As seen in this Vaccine Safety Datalink study, a high proportion received at least two doses, but only 54% completed the required three-dose series.

In another study in adults at very high risk for HBV infection, such as MSM with sexually transmitted diseases, only 43% completed the vaccine regimen, and some of those took up to 5 years to complete.

Because both current vaccines require all three doses over a 6-month period for most persons to achieve seroprotection, many adults fail to complete the full course and are left

unprotected and at risk.

Because that third dose is needed, most adults remain at risk for a prolonged period of time between even the second and the third dose. Among adults who only get two doses, only 20 to 50% achieved seroprotection. In other words, 50 to 80% remain susceptible to hepatitis B. This is a concern for those at imminent risk of infection, such as healthcare providers, first responders, and travelers.

So what would an improved hepatitis B vaccine in adults look like? To me, such a vaccine would induce high seroprotection in all adults, especially those nonresponsive to the current vaccines. An improved vaccine would require fewer doses given over a shorter time than the current 3-dose/6-month regimen. And, of course, equally important is that any new vaccine maintain the safety profile of the current vaccines.

Clinicians need confidence that they can protect adults quickly and reliably. Adults are not optimally served by the current vaccines. Adults deserve better. They need a vaccine that induces immunity rapidly, reliably, and at high levels of seroprotection.

Thank you. And I'm happy to introduce Dr. Stanley Plotkin.

DR. EDWARDS: Are there questions for Dr. Schaffner before we go on to Dr. Plotkin?

DR. PORTNOY: Yeah, this is Dr. Portnoy. I'm not sure if there's a way for me to raise my hand by telephone, but I was just wondering how long does the immunity last? In these children up to 19 who get immunized primarily, does it confer lifetime immunity, or does the immunity wane over time?

DR. SCHAFFNER: Yes, the immunity at the moment appears to be virtually lifetime. So I think we can assure ourselves there are no recommendations for routine reimmunization needs.

DR. EDWARDS: Other questions?

(No response.)

DR. EDWARDS: Okay, Dr. Plotkin will discuss the mechanism of action. Dr. Plotkin is Emeritus Professor at the University of Pennsylvania and member of the Board of Directors of Dynavax.

Stanley.

DR. PLOTKIN: Well, thank you, Kathy. And yes, I am on the board of Dynavax. I joined the board in 2005 because it became clear to me that the success of many future vaccines will depend on new adjuvants, in particular because of the issue of immunosenescence, which is obviously important for adult vaccines, and I think adjuvants are key to solving that.

So in the next few slides, I will describe the adjuvants a little bit more extensively than Dr. Major has, which is called 1018, and summarize our current understanding of its mechanism of action.

So the adjuvant 1018 is a small, synthetic, single-stranded oligonucleotide with specific CpG sequence motifs that mimic the natural innate immune response to bacterial and viral DNA. This innate response activates antigen-presenting dendritic cells, leading to enhanced B and T cell responses to co-administered vaccine antigens.

The actions of 1018 are mediated by its interaction with the toll-like receptor 9, which you've heard about. And as you know, the toll-like receptors are among the most important innate immune receptors for sensing the presence of invading microorganisms and viruses.

This diagram shows the TLR receptors, and they provide essential signals for the initiation of T and B cell responses.

There are other adjuvants that act through toll-like receptors. For example, Cervarix, the human papillomavirus vaccine, targets one of those receptors, TLR4, and Cervarix has been approved in multiple countries and has proven to be very safe and effective.

Now, there are four toll-like receptors localized to the endosomes rather than the cell membranes, and they all recognize nucleic acids. One of these is TLR9, which recognizes the specific CpG nucleotide motifs commonly found in bacterial and viral DNA; 1018 represents an optimized synthetic agonist for TLR9.

While Heplisav would be the first vaccine to specifically

target TLR9, there are widely used vaccines that contain DNA and engage TLR9 as one of the immune activation signals they deliver. These include Zostavax, the zoster vaccine, yellow fever vaccine, and BCG.

Now, let me summarize our understanding of the key events that follow the injection of Heplisav-B containing 1018.

In the first 1 to 2 days after injection, 1018 and the hepatitis B surface antigen are concentrated at the injection site and in the draining lymph node; 1018 binds to TLR9 and activates the plasmacytoid dendritic cells that secrete interferons and cytokines such as IL-12, as well as to present hepatitis B surface antigen peptide fragments to helper T cells. These helper T cells, in turn, provide essential signals to B cells that recognize intact hepatitis B surface antigen.

Over the next week or two, the concentrations of 1018 and hepatitis B surface antigen steadily decline. However, T and B cells continue to proliferate in germinal centers, and these cells develop into antibody-producing plasmablasts. It's important to say that by about 2 weeks, 1018 has been effectively cleared from the immune system.

The germinal centers gradually contract, and plasmablasts develop into mature plasma cells and greatly increase their antibody production. Plasma cells ultimately migrate to the tissues and continue to produce circulating antibodies to

hepatitis B surface antigen.

Now, if this scheme looks familiar, it is because the basic principles of the adjuvant activity of 1018 are the same as for most other adjuvants. Virtually all successful adjuvants work through local activation of short-lived innate immune responses that promote effective antigen presentation to helper T cells. This then leads to enhanced antibody production and the generation of durable T and B cell membranes.

1018 is distinctive in that it targets a single well-characterized receptor and a specific subset of plasmacytoid dendritic cells. In fact, 1018 improves upon alum, not by being more potent or long lived but by being uniformly active in nearly all subjects and being much less compromised by age and health status.

Now, while the actions of 1018 are focused at the injection site and draining lymph node at the doses used in Heplisav-B, toxicology studies using repeated high doses of 1018 allow us to evaluate the potential systemic effects of 1018. 1018 was given weekly to monkeys at doses up to 270-fold greater than used in Heplisav and were generally well tolerated. The findings in major target organs of the monkeys, such as spleen and liver, were largely consistent with TLR9-mediated immune stimulation and were reversible after 4 weeks. More specifically, there were no effects on the cardiovascular

system and no findings that suggested a mechanism for 1018 to cause cardiovascular events.

So these findings in toxicology studies were largely explained by known features of TLR9 biology, and studies of TLR9-deficient mice failed to show evidence of off-target effects.

Lastly, in clinical studies of 1018 in therapeutic applications, repeated doses up to 100 mg, which is 33 times the 3 mg Heplisav dose, have been safely given, and no maximum tolerated dose was reached.

I've been a board member of Dynavax for 12 years because I believe that its research on new adjuvants offers significant benefit for adult patients who need protection from hepatitis B in this case.

I believe this potential public health is well reflected -- potential for public health is well reflected in the Heplisav data being presented to you today. But as you know, the final pivotal trial did show a numerical imbalance in a cardiovascular term that the Committee will, without doubt, discuss today.

But Dynavax proposes a comprehensive postmarketing surveillance study which, I assure you, I and other board members support as appropriate, responsible, and offering us the fastest means to further demonstrate the safety of Heplisav-B.

I want to give you my personal assurance, and that of the entire board of Dynavax, that we support the proposal and will ensure that management has the necessary financial and other support to deliver this commitment.

Thank you. I now turn it back to Dr. Janssen.

DR. LEVY: A question.

DR. EDWARDS: Are there questions for Dr. Plotkin?

DR. LEVY: Yes.

DR. EDWARDS: Ofer.

DR. LEVY: Yes. Hi. Thank you, Stan, for a very clear and helpful presentation. As I understand it, the Heplisav vaccine is composed of the antigen with the adjuvant co-added, not linked to the antigen.

What studies have been done, and I'm sure some have been done, to know whether the adjuvant gets into the systemic circulation at all in rodents, in nonhuman primates, and/or in the human clinical trials, and whether there are any changes in white blood cell composition in the peripheral blood when this is administered?

DR. PLOTKIN: Good questions. I think I'll ask Bob Coffman, the Chief Scientific Officer of Dynavax, to answer that.

DR. COFFMAN: Yes, thank you. I'm Bob Coffman, Chief Scientific Officer at Dynavax.

We do have studies in one of the Heplisav studies. We did

measure the appearance of 1018 in circulation. It peaks at about 1 hour. It is detectable, but barely, in circulation. It peaks at about 1 hour. It declines rapidly, barely detectable in a few individuals at 4 hours, and it basically disappears after that. Now, that's not surprising.

Oligonucleotides basically don't circulate multiple rounds; they get taken up by livers and spleens. But, of course, it's greatly diluted at that point. Keep in mind it's well below, by our measurements, levels that would be systemically active.

DR. LEVY: Right. And then in terms of white blood cell composition, do you see any shift in total leukocytes or differential in the peripheral blood in subjects?

DR. COFFMAN: There are small shifts, usually more readily observable in our therapeutic studies with higher doses of CpGs. There's sort of transient lymphocytopenia and neutropenia. Most of the people in the field think it's due to margination because it comes back very quickly. So there are not long-term shifts in blood cells that we or really anyone else in the field has reported with this sort of therapy.

DR. BENNINK: Yeah.

DR. EDWARDS: Dr. Bennick.

DR. BENNINK: For M1 -- excuse me. Were M1 macrophages looked at, at all? Is there any activation of them?

DR. COFFMAN: They haven't been looked at, but macrophages

and monocyte lineage cells are not responsive to TLR9. So direct activation, certainly in a short term, does not seem to occur with CpGs.

DR. BENNINK: But indirect through interferon or other aspects with --

DR. COFFMAN: Sure, sure. The interferon induces -- will obviously induce responses in monocyte, macrophage, lineage cells. We haven't really tried to look at the -- particularly in a vaccine setting. We look at that more right now in the context of other studies with different CpGs in tumor immunotherapy studies.

DR. BENNINK: Yeah. And in the monkey studies, were blood vessels taken out or anything else in terms of looking -- the heart taken out and looked at, at all, in terms of those things?

DR. COFFMAN: As is typical in toxicity studies like that, there's gross examination of a wide variety of tissues, a histological examination of a number of specific tissues, including, I believe, the heart is one of these. And if nothing is really found, you know, further investigation isn't dug into. The heart's not really a target organ for oligonucleotides per se.

Now, in terms of the vasculature, other than seeing gross differences, I don't think any specific histology on the vasculature was done in any of these tox studies. It's not

typical.

DR. PACKER: One more?

DR. EDWARDS: Dr. Packer and Dr. Hoofnagle.

DR. PACKER: One question. I understand that TLR9 stimulates interleukin-1 beta. Do you have data on that process in your trials or in animal studies?

DR. JANSSEN: We haven't looked at it, but Bob, do you want to comment on that?

DR. COFFMAN: Yes. Bob Coffman.

Stimulation studies in in vitro, looking at responses in both whole peripheral blood cells and individual cell types, interleukin-1 beta, although it is stimulated a little bit, it's not a prominent part of the response. I mean, a great majority of the cytokine response is initially Type I interferons followed by -- particularly by IL-12, which is particularly an important cytokine here. So compared to alum stimulation, which is a very strong stimulator of IL-1 beta, for example, it's not a big player.

DR. EDWARDS: Dr. Hoofnagle.

DR. HOOFNAGLE: Have you done a study where you gave the adjuvant and the hepatitis vaccine in separate sites to show that they need to be mixed rather than --

DR. COFFMAN: Bob Coffman.

We at the company have not done that. A couple of the scientific founders of the company way back in the '90s did

several types of studies like that, and others in the field have, putting an adjuvant in mice mostly, obviously. Putting an antigen in one limb and the adjuvant in the other, you have no adjuvant effect.

Delaying it more than a few days, you know, if you delay a week or two delivering the antigen after the adjuvant, you have very little adjuvant effect. So, yes, they do need to be co-administered. I think that's kind of what one would expect.

DR. EDWARDS: Any other questions?

(No response.)

DR. EDWARDS: Okay. Would you like to go forward, then, Dr. Janssen, to discuss the immunogenicity and safety and postmarketing plan?

DR. JANSSEN: Thanks, Dr. Plotkin.

I'll now present our immunogenicity results for Heplisav from our three Phase 3 pivotal trials, and they demonstrate that Heplisav achieves significantly higher and earlier seroprotection using fewer doses in all adult populations. This includes subpopulations who have reduced seroprotection rates with the current vaccines.

The Heplisav clinical development program, like other clinical development programs for hepatitis B vaccines, used seroprotection as the measure of clinical efficacy and basis for licensure.

Seroprotection is defined as the level of antibodies

against hepatitis B surface antigen, or anti-HBs, greater than or equal to 10 mIU/mL.

Now, it's important to recognize that unlike with many other vaccines, once a healthy person achieves an anti-HBs level greater than 10, protection lasts for at least 30 years even if the antibody level drops below 10.

Now, the indicator of seroprotection in a population is the seroprotection rate, or SPR. Now, that's the proportion of persons who are seroprotected at a specific time point.

Our three pivotal trials are HBV-10, HBV-16, and HBV-23, our most recent trial. In each of these trials, different randomization ratios were used, ranging from 2:1 to 4:1.

The three trials shared common design features. All three trials were observer-blinded, they were randomized, they were active-controlled, and they were multicenter. Trial participants could not have evidence of current or previous hepatitis B infection, and they could not have received a hepatitis B vaccine prior to enrollment in the trial. Persons with HIV or immunosuppression or history of autoimmune disease were also excluded.

The demonstration of seroprotection relied on head-to-head comparison between Heplisav and Engerix in adults. Now, we chose Engerix as the comparator vaccine in all our pivotal trials because it's the hepatitis B vaccine that induces the highest seroprotection rates in adults and is the most

frequently used by clinicians in the United States.

The Heplisav group received doses at 0 and 1 month, along with a placebo dose at 6 months. The Engerix group received doses at 0, 1, and 6 months. Lastly, concentrations of antibodies to hepatitis B surface antigen were measured using an approved standardized commercial assay.

All trials were designed and powered for the primary endpoint to demonstrate the non-inferiority of the SPR of Heplisav compared with Engerix. The pre-specified non-inferiority margin of 10 percentage points was based on historical Engerix data and agreed to by regulatory authorities.

Non-inferiority was met if the lower bound of the 95% confidence interval of the difference in SPRs was above -10%. A statistically significantly higher SPR was achieved if the lower bound of the confidence interval was greater than zero.

In the immunogenicity comparisons, the per-protocol population was chosen for the primary endpoint analyses in all three trials. It was defined prior to unblinding, and it consisted of all subjects who received all three injections within the pre-specified clinic visit time frame. They had no major protocol deviations that could affect immunogenicity, and they had anti-HBs concentrations obtained at baseline and then within visit windows at the primary endpoints.

I'll now review the results of each of our three trials,

starting with HBV-10. HBV-10 enrolled subjects 11 to 55 years of age in Germany and Canada; 2,415 adults were randomized in a 3:1 ratio to receive Heplisav or Engerix, and they were followed for 28 weeks after the first injection.

The top three reasons for excluding subjects from the per-protocol population across both of the groups include serum collection and vaccination outside the visit window and no anti-HBs results at the primary endpoint. In total, 83.5% of the Heplisav group and 86% of the Engerix group were included.

Demographic and baseline characteristics were generally balanced between the two treatment groups by age, sex, race, BMI, and smoking history, and they were not expected to bias the immunogenicity results. The mean age was 40 years in this trial.

The primary endpoint of HBV-10 was to demonstrate the non-inferiority of the SPR induced by Heplisav at Week 12, and that's 8 weeks after the last dose, to the SPR induced by Engerix at Week 28, which is 4 weeks after the last dose.

The primary endpoint was met. The SPR in the Heplisav group was non-inferior to that in the Engerix group, and it was statistically significantly higher. The SPR in the Heplisav group at Week 12 was 95%; in the Engerix group at Week 28, 81.2%. The difference between SPRs was 13.7%, with the lower bound of the 95% confidence interval of the difference in SPRs of 10.4%.

In a post hoc analysis, the peak SPR within the trial occurred at Week 24 in the Heplisav group, and it was significantly higher than the peak SPR in the Engerix group, which occurred at Week 28. Now, it's also important to note that Heplisav achieved the same SPR much earlier, at Week 8, that Engerix reached at Week 28.

Now, let's turn to Study 16. This compared the immunogenicity and safety among healthy adults 40 to 70 years of age in the United States and Canada; 2,452 adults were randomized in a 4:1 ratio to receive Heplisav or Engerix, and they were followed for 52 weeks after the first injection.

The top three reasons for excluding subjects from the per-protocol population across both of the groups included vaccination and serum collection outside the visit window and not receiving all study injections. In total, 77.8% of the Heplisav group and 73.1% of the Engerix group were included.

Demographics in Study HBV-16 were balanced between the treatment groups and not expected to affect immunogenicity results. The mean age was 54 years.

The primary objective of the HBV-16 was to demonstrate the non-inferiority of the SPR at 8 weeks after the last dose; that was Week 12 for Heplisav and Week 32 for Engerix. The primary endpoint in the Engerix group was 4 weeks longer than the endpoint in HBV-10, as was requested by FDA.

A key secondary endpoint was to demonstrate that the

Heplisav SPR at the primary endpoint was statistically significantly higher than the Engerix SPR.

Similar to HBV-10, HBV-16 met its primary endpoint, demonstrating that seroprotection with Heplisav is non-inferior to that of Engerix. In HBV-16, the SPR in the Heplisav group at Week 12 was 90.1%, and in the Engerix group at Week 32, 70.5%. The difference between SPRs was 19.6%, with a lower bound of the 95% confidence interval of 14.7%. Additionally, Heplisav achieved its key secondary endpoint of a statistically significantly higher SPR.

Now, similarly to HBV-10, in a post hoc analysis, the peak SPR induced by two doses of Heplisav was significantly higher than the peak SPR induced by three doses of Engerix. Again, Heplisav achieved the same SPR much earlier, that is, at Week 8 compared with Week 28 for Engerix.

Now, let's turn to Study HBV-23. It compared the safety and immunogenicity in adults 18 to 70 years of age in the United States; 8,374 adults were randomized in a 2:1 ratio to receive Heplisav or Engerix, and they were followed for 56 weeks after the first injection. Immunogenicity was measured only at Weeks 24 and 28.

The top three reasons for excluding subjects from the per-protocol population across both groups included no anti-HBs results at the primary endpoint, not receiving all study injections, and taking prohibited medications. In total, 81.1%

of the Heplisav group and 82.3% of the Engerix group were included.

In HBV-23, demographic and baseline characteristics were balanced across the treatment groups. The mean age was 50 years with greater racial diversity than in our previous trials. About a quarter of the subjects were black or African American in each arm. Adults in this trial had a higher BMI and a higher prevalence of diabetes than in the other two trials.

The primary endpoints of HBV-23 were to evaluate the overall safety of Heplisav with respect to clinically significant adverse events and to demonstrate the non-inferiority of the SPR induced by Heplisav compared to the SPR induced by Engerix at Week 28 in adults with Type 2 diabetes mellitus. The secondary endpoint included a non-inferiority analysis comparing the Heplisav SPR and Engerix SPR in all subjects and in pre-specified subpopulations.

HBV-23 met its primary endpoint, demonstrating that seroprotection with Heplisav is non-inferior and statistically significantly higher than Engerix in adults with Type 2 diabetes. In this population, the SPR in the Heplisav group at Week 28 was 90%, and in the Engerix group at Week 28 it was 65.1%. The difference between SPRs was 24.9%, with the lower bound of the 95% confidence interval of 19.3%.

Turning to the results of the secondary endpoints,

seroprotection for Heplisav was higher than Engerix in the total population in each of the pre-specified subpopulations. This is including all age groups, from 100% versus 93.9% in the youngest adults, to 91.6% versus 72.6% in the oldest group. Overall, the SPR in each of these pre-specified subpopulations is consistently greater than 90% in the Heplisav group. Differences in seroprotection for Heplisav were also statistically significant in all these pre-specified subgroups compared with Engerix.

This forest plot shows the point estimates and 95% confidence intervals of the differences of the SPRs that I showed on the previous slide. The vertical line at -10% is indicative of non-inferiority, and the vertical line at zero is indicative of statistical significance. The largest differences between Heplisav and Engerix are in populations that have been reported to have reduced seroprotection from alum adjuvant in vaccines. However, the seroprotection rates are significantly higher in Heplisav recipients in all the pre-specified subgroups.

When we look by race and ethnicity, the peak SPR in the Heplisav group was non-inferior to the Engerix group in each racial or ethnic group except in a few Pacific Islanders. We did not see variability in the SPR in the Heplisav group.

In summary, in all three pivotal trials, Heplisav demonstrated non-inferiority and significantly higher

seroprotection rates at the primary endpoints using fewer doses in all adult populations. Also, in trials HBV-10 and 16, Heplisav achieved SPRs by Week 8 that Engerix achieved only at Week 28.

Now let's move to safety.

DR. EDWARDS: Are there any immunogenicity questions before we move to safety? Jack.

DR. BENNINK: Yeah, do you have any data at all on HBV-23, as to whether any of the people in the study, in either group, received an infection later? After the study began, did any of them become infected with HBV?

DR. JANSSEN: Not that we're aware of. We did not systematically look at that.

DR. EDWARDS: Janet.

DR. ENGLUND: I'm wondering if you have any data from any of your trials on the duration of antibody response.

DR. JANSSEN: Well, these trials -- this HBV-23 went for a year but -- I'm sorry, HBV-16 went for a year, and we have antibody levels in that. But we did look -- we've done a CKD trial and did a Phase 3 CKD trial in about 500 subjects. These were randomized 1:1, and we did follow some of those subjects, a subset of those subjects, over about 2½ years, and what this shows is the antibody decay curves of Heplisav and Engerix are essentially the same. The Heplisav curve is statistically significantly higher than the Engerix curve.

DR. EDWARDS: Dr. Sawyer.

DR. SAWYER: You mentioned exclusions for taking medications that were prohibited in the clinical trials. What were those medications?

DR. JANSSEN: Primarily systemic steroids.

DR. EDWARDS: Dr. Levy.

DR. LEVY: Realize that the antibody is clearly the correlative protection you're going after here, but as an exploratory, did you also look at cell-mediated immunity?

DR. JANSSEN: We did not, no.

DR. EDWARDS: Dr. Hoofnagle.

DR. HOOFNAGLE: The smokers, was that current smokers or anytime smokers?

DR. JANSSEN: No, it's current smokers.

DR. EDWARDS: Other immunogenicity questions?

(No response.)

DR. EDWARDS: Okay, then please proceed.

DR. JANSSEN: The Heplisav clinical development program demonstrated that Heplisav is generally well tolerated, with an overall acceptable safety profile compared with the most commonly used licensed hepatitis B vaccine.

Dynavax enrolled more than 14,200 adults in 11 completed clinical trials, including more than 10,000 subjects who received Heplisav and 4,200 subjects who received Engerix.

We'll present integrated safety data today for our three

pivotal Phase 3 trials, and they comprise 93% of our safety database. The data from the total safety database were consistent with the results from the pivotal trials.

Now I'll present our safety data using three different populations. It's important to note, as you look at the results, that none of the trials were randomized 1:1. The safety populations for HBV-10 and HBV-16 will be used to show solicited reactogenicity results and unsolicited adverse events.

The safety population for HBV-23 will be used to show unsolicited medically attended adverse events, that is, events for which subjects sought medical care.

The primary safety population, or PSP, comprises adults 18 to 70 years of age in the two previous trials, HBV-10 and 16, and also the new trial, HBV-23. The PSP had a subject allocation ratio of 2.4:1.

Now, the PSP has the largest sample size with the most events and provides the most reliable estimates. It will be used to evaluate immune-mediated adverse events, deaths, and SAEs in the three pivotal trials. First, I'll describe reactogenicity and adverse events in HBV-10 and 16.

Around 55% of subjects in both vaccine groups had a solicited post-injection reaction. The frequency of adverse events and discontinuation was balanced between the two treatment groups. Heplisav was generally well tolerated, with

no cases of vaccine-associated anaphylaxis or other serious post-injection reactions. Most solicited post-injection reactions were mild or moderate in severity, they were self-limited, and they resolved within 7 days after injection.

In this analysis following all active injections, the frequencies of local post-injection reaction overall were balanced between the two groups. The most frequent local reaction in both groups was injection site pain.

In the Heplisav group, 32% of subjects had a systemic post-injection reaction compared with 37% of subjects in the Engerix group. Now, the most frequent systemic reactions in both of the groups were fatigue and headache followed by malaise. With both vaccines, there was decreasing reactogenicity with successive doses.

In HBV-23, the proportion of subjects who experienced a medically attended adverse event or discontinued treatment due to an MAE was balanced between the groups.

At the preferred term level, assessing whether small numerical imbalances between treatment groups represent true and clinically meaningful treatment effects or random variation is a consistent challenge in clinical development. While randomized clinical trials are our best tool for understanding differences between interventions, they have limitations, particularly when they're not powered to evaluate events that are reported in very small numbers.

Now, because none of the events we will discuss were pre-specified endpoints, we did not do formal statistical testing because the p-value is uninterpretable in this setting. Instead, to identify events that required further clinical and epidemiologic assessment, we selected those for which the 95% confidence intervals of the relative risk excluded 1, as well as those with a large relative risk even if the 95% confidence interval included 1.

In HBV-23, of the 1,405 unique MAE preferred terms reported, 10 had 95% confidence intervals that excluded 1. Only one event occurred with a higher frequency in the Heplisav group: herpes zoster. Now, herpes zoster is an event mechanistically more likely to be prevented by stimulating TLR9.

Nine MAEs occurred at a higher frequency in the Engerix-B group. None of the nine MAEs in the Engerix group had previously known -- been known to be associated with Engerix and none have a known biologically plausible explanation.

Of the 1,405 MAEs reported, 19 had relative risks greater than 6. All these events had 95% confidence intervals that included 1.

Five MAEs occurred at a higher frequency in the Heplisav group. Of the five in the Heplisav group, we particularly investigated acute myocardial infarction and will present those data after immune-mediated AEs and deaths.

Fourteen MAEs occurred at a higher frequency in the Engerix group. Six are on this slide. Eight events with a lower relative risk of 6 are not shown on this slide but were presented in the briefing book. None of the 14 events in the Engerix group had previously been associated with Engerix.

From a statistical perspective, given the large number of MAE terms reported in the study, one expects a small number of events will have 95% confidence intervals that exclude 1 or high relative risk even though there is no true relationship to vaccine. This is especially true for events reported in small numbers.

Now, let's look at the integrated safety data. Overall in the PSP, immune-mediated events were 0.2% and 0.13%, and deaths were 0.28% and 0.21% in the Heplisav and Engerix groups, respectively. SAEs were balanced between vaccine groups.

In the Heplisav clinical development program, safety assessments were designed to identify evidence of any autoimmune disease using three assessment methods.

First, we performed a systematic database search for immune-mediated adverse events of special interest using a pre-specified list provided by FDA, and this comprises autoimmune, autoinflammatory, and hypersensitivity reactions. The list is provided in your briefing book.

During HBV-16 and HBV-23, potential new onset immune-mediated diseases, including those on the list of adverse

events of special interest, were evaluated by a blinded, independent safety evaluation and adjudication committee, or SEAC.

The SEAC comprised three experts from the Mayo Clinic, including two experts in autoimmune disease, one of whom, Dr. Ytterberg, is here with us today, and the third member was an ID physician, Dr. Poland, who's also here with us today. All identified events were reviewed for confirmation and new onset.

Finally, we performed laboratory assessments of autoantibodies as either pre-specified analyses or retrospective analyses in certain trials.

In the primary safety population, the most frequent new-onset immune-mediated event was Bell's palsy, occurring in 0.06% of the Heplisav group, 0.05% in the Engerix group. The only other event that occurred in more than one Heplisav subject was hypothyroidism.

A variety of other AESIs other than Bell's palsy occurred in each of the groups. In the PSP, new-onset AESIs, excluding Bell's palsy, occurred in 0.11% of the Heplisav group and 0.08% of the Engerix group. Grave's disease was the only event to occur in both of the treatment groups. The remaining immune-mediated events occurred in one subject each. They involved a variety of organ systems, most frequently including the skin or nervous system.

We used a classification system based on pathophysiology, instead of organ systems, that was proposed by authors at CBER for use in understanding potential immune-mediated events that may occur following vaccination. Now, excluding Bell's palsy, the AESIs observed in the three pivotal trials are quite diverse, both in the time of onset as well as in their principal mechanisms of pathogenesis. Some are characterized by cell-mediated autoreactivity, such as vitiligo and Grave's; others by autoantibodies, such as the ANCA-positive vasculitides; still others by a variety of innate or inflammatory mechanisms.

Now, this pattern of AESIs does not suggest a common mechanism and is more consistent with a gradual accumulation of unrelated events over the course of the safety monitoring period. Notably absent from this list are diseases known to be linked to nucleic acid recognition by toll-like receptors, such as lupus, Sjogren's, and dermatomyositis. Thus, the data suggests that Heplisav does not increase the risk of any specific autoimmune mechanism.

This is an example where an imbalance in overall AESIs in HBV-16 and 23 was not clinically meaningful when you look at the individual disparate events. In the primary safety population that had the subject ratio of 2.4:1, rare serious immune-mediated AEs were balanced with three in the Heplisav group and one in the Engerix group. In the Heplisav groups,

one event of granulomatosis with polyangiitis; this was diagnosed over 2 months after the last Heplisav dose.

The event of Guillain-Barre syndrome occurred more than 3½ months after the last Heplisav dose and 5 days after an influenza vaccination. The event of cavernous sinus syndrome is thought to be an inflammatory condition of Tolosa-Hunt syndrome but was not confirmed radiologically. This occurred 8½ months after the last Heplisav injection.

In the Engerix group, one rare serious immune-mediated AE of microscopic polyangiitis, an ANCA-positive vasculitis, was reported.

HBV-23 was conducted because the size of the safety database was considered too small to detect an imbalance in uncommon immune-mediated events. In particular, FDA expressed concerns because of two rare events.

In HBV-23, a secondary objective was to describe the incidence of those events, granulomatosis with polyangiitis and Tolosa-Hunt syndrome, two distinct pathologic entities. In a trial that was larger than the two previous studies combined, neither GPA nor THS occurred in HBV-23.

Finally, as a part of our immune-mediated disease assessment, we saw similar autoantibody development in Heplisav recipients compared with Engerix recipients.

Anti-neutrophil cytoplasmic antibody, or ANCA, testing was performed retrospectively because of the event of

granulomatosis with polyangiitis in HBV-10. More than 2,500 subjects were evaluated, and there were no confirmed positive results other than the previously mentioned ANCA-positive vasculitis cases that occurred in each arm.

Anti-nuclear antibody, or ANA, testing was performed as a protocol-specified assessment in more than 5,200 subjects; 5.5% of Heplisav, 5.1% of Engerix subjects developed these antibodies during the trial.

Anti-double stranded DNA testing was performed also as a protocol-specified assessment; 1.2% of Heplisav and 1% of Engerix subjects developed such antibodies.

Overall, the autoantibody data demonstrate that changes in ANCA, ANA, and anti-double stranded DNA were similar between the groups.

In HBV-23, we conducted a lab sub-study of anti-phospholipid antibodies because of the numerical imbalance in pulmonary emboli in the previous BLA submission, in which 0.11% of Heplisav subjects and no Engerix subjects had pulmonary embolus. Of note, pulmonary emboli were balanced between the treatment groups in HBV-23, 0.05% in the Heplisav group, 0.07% in the Engerix group.

In the lab sub-study in HBV-23, 207 Heplisav subjects, 102 Engerix subjects were tested for a panel of anti-phospholipid antibodies shown on this slide. Results of the sub-study showed that these new onset anti-phospholipid antibodies were

relatively uncommon and were balanced between the groups.

The proportion of subjects who developed elevated anti-beta-2 glycoprotein 1 IgM levels was higher in the Heplisav group than in the Engerix group at Week 8. Importantly, there was no difference in any beta-2 glycoprotein 1 IgG. Isolated elevation of anti-beta-2 glycoprotein 1 IgM has not been associated with thrombotic disease in the literature, and in this study, no one with an elevated anti-beta-2 glycoprotein 1 IgM had a thrombotic event.

Now I'll review deaths. In HBV-23, there was a numerical imbalance in total deaths between the groups. The difference was not seen in HBV-16, with one death in each group.

Except for deaths due to drug overdose, causes of death were similar between the groups, including cardiovascular deaths. All other deaths occurred in only one subject in either of the treatment groups. No death was considered related to study treatment. Most deaths occurred in subjects with significant preexisting diseases or contributory social circumstances.

In the Heplisav group, four of the six overdose deaths involved cocaine, and two were prescription drug overdoses. The manner of death was accidental in the four subjects in whom it was determined. The subject in the Engerix group died of a fentanyl overdose.

In the primary safety population, the percentage of

subjects reporting any SAE was 4.8% in both of the groups. SAEs were generally similar between the Heplisav and Engerix groups, but I want to highlight two notable imbalances. A higher proportion of Heplisav recipients than Engerix recipients experienced an SAE of acute myocardial infarction, and a higher proportion of Engerix recipients experienced an SAE of prostate cancer. The magnitude of the differences between treatment groups for these two events was similar but in opposite directions. These are typical examples of observing unexpected post hoc findings in a large database.

Now let's look more closely at the numerical imbalance in myocardial infarctions in individual trials. In HBV-23, we identified a numerical imbalance in safety events coded to the single MedDRA-preferred term of acute myocardial infarction. However, in HBV-16, we did not see the same difference between groups.

Now, in fact, while the numbers were small, there was a lower proportion of subjects in the Heplisav group than in the Engerix group, who had an acute myocardial infarction. There were no MIs in HBV-10, which enrolled a younger population than HBV-16 or HBV-23. We were surprised by the numerical imbalance in myocardial infarction in HBV-23.

There was no evidence of cardiac toxicity in preclinical toxicology studies. And since no such finding was observed in previous clinical trials, it was not prospectively evaluated in

HBV-23.

Finally, there is no known plausible association between cardiovascular disease and 1018, other CpGs, or other hepatitis B vaccines.

Because of the medical importance of the preferred term, we sought to thoroughly investigate and understand this observation. We engaged an external cardiologist who's an expert in myocardial infarctions in clinical trials, and I want to now ask Dr. Darren McGuire to describe his assessment of the imbalance.

DR. EDWARDS: Before that, are there any questions of the safety data that have been presented, before we go to the cardiovascular?

DR. LEVY: Well, I had a question. In your last slide, you mentioned no known plausible associations, but there are some studies looking at toll 9 signaling from mitochondrial DNA and cardiac inflammation. Are you familiar with those?

DR. JANSSEN: No. I'd like to ask Dr. Coffman, though, to comment.

DR. EDWARDS: We'll defer that question. Okay, all right. Cardiovascular safety, then. Sorry.

Okay, please.

DR. COFFMAN: Yeah, I'll make it quick. Bob Coffman, Dynavax.

I think the studies you're referring to, Dr. Levy, are

several studies in -- showing TLR9 expression, TLR9 responses by cardiac myocytes, and we're familiar with those studies.

Now, I'll get ahead of Dr. McGuire here but just tell you what I think he'll present is pretty clear evidence that none of the events that are scored as myocardial infarction were due to any form of cardiomyopathy. And again, I'll stress -- I mentioned once before, the heart is not a target organ. Even in the high-dose toxicology studies, you don't see actual meaningful or even detectable concentrations of CpGs concentrating in the heart.

DR. EDWARDS: Dr. Packer.

DR. PACKER: Yeah, I really don't want to get into mechanisms that I don't understand, but if I understand correctly, when we're talking about myocardial infarction, the organ that we're worried about is not the myocyte -- is not the heart. It's the plaque, it's the atherosclerized plaque. If I understand correctly, toll-like receptors have been implicated in plaque, both stability and instability. Would that be fair?

DR. JANSSEN: Dr. Coffman.

DR. COFFMAN: Certainly toll-like receptors 2 and 4 have been very much implicated both in development of atherosclerosis and in various aspects of plaque instability. Now, TLR9, the data are much less clear there, one or two reports that there are -- that one can detect plasmacytoid dendritic cells, being about the only TLR9 positive cells in

plaques. You can detect them in plaques; they can be isolated and behave sort of like we expect from pDCs.

But TLR9 expression actually, in most parts of the vasculature, normal as well as in plaques, is really one of the -- lower than most of the other TLRs. TLR2 and TLR4 in particular are much higher and much more clearly implicated in all phases of cardiovascular disease.

DR. PACKER: I just wanted to make a point. It's very interesting, cardiologists, when they look at myocardial infarction, don't think of it as sort of a heart disease. It's a vascular disease, and the two primary drivers of myocardial infarction are inflammation, plaque inflammation and thrombosis. So to focus when we look at myocardial infarction is to look at factors that drive inflammation and thrombogenesis.

DR. EDWARDS: Okay. So let's go on, then, to the cardiovascular safety. Dr. Darren McGuire, Professor of Medicine at the University of Texas Southwestern Medical Center.

Dr. McGuire.

DR. McGUIRE: Thank you. Good morning. I'm Darren McGuire, Professor of Medicine at the University of Texas Southwestern Medical Center and Deputy Editor of the journal *Circulation*. I'm a general cardiologist and clinical trialist with extensive experience in the design and conduct of

cardiovascular outcomes trials, clinical trial event adjudication, and work on independent data monitoring committees of cardiovascular outcome trials. I am a former member of the FDA Cardiovascular and Renal Drugs Advisory Committee and maintain special government employee status as an ad hoc consultant for FDA.

Dynavax asked me to help them assess the imbalance of acute myocardial infarction observed in one of the Heplisav Phase 3 trials. When I see unexpected imbalances in study data, I first want to know if the events are occurring more frequently than would be expected and do they occur in patients expected to have such events? Second, I want to know how consistent is the imbalance, has it been observed in other studies or populations with the same or similar exposure? Third, I want to know if the occurrence of any related events also demonstrate imbalances similar in magnitude and/or direction. Fourth, I'm interested if there is any pattern of the association with regard to the timing of the exposure and, when possible, any difference in the imbalance with increasing dose of exposure. Lastly, based on existing knowledge with regard to the relevant science and biology, I explore any plausible mechanistic links that may exist to explain the imbalance.

To explore the MI imbalance observed in HBV-23, I set out on a five-part strategy. I asked the Sponsor to model expected

event rates using available risk prediction models commonly used in clinical practice, applied to the enrolled cohort characteristics. These data were used to assess observed rates in the context of expected background cardiovascular events. I also requested blinded clinical annotations and, when possible, cardiac catheterization reports for each of the reported acute myocardial infarction events for my personal review. To cast a broader net for all potential atherosclerotic cardiovascular events, I asked the Sponsor to perform Standardized MedDRA Queries or SMQs for both MI and for stroke. Additionally, I encouraged the Sponsor to engage a group experienced in cardiovascular outcomes trials, to perform central, blinded adjudication of all the reported cardiovascular events, and to expand the analysis of cardiovascular events using the gold standard composite outcome used in most atherosclerotic cardiovascular disease trials, referred to as major adverse cardiovascular events, or MACE. I considered possible vaccine-induced immunologic etiologies that might underpin increased risk for myocardial infarction and assessed if any temporal associations were evident between vaccine administration and reported acute myocardial infarction and MACE events.

Let me review what I found. First, I assessed how the observed cardiovascular event rates in the Heplisav patients compared with predicted rates of adverse cardiovascular outcomes and specifically myocardial infarction. To assess

this, the Sponsor estimated the expected incidence of cardiovascular events using cohort characteristics based on age, sex, and race, comparing observed versus expected events. In each comparison, the observed incidence rate per thousand person-years of follow-up in the Heplisav group was similar to or lower than predicted.

The expected rate of myocardial infarction in the studies was 2.6 per 1,000 person-years. It was 2.4 in the Heplisav group but only 0.7 in the Engerix group, nearly fourfold lower than expected. In HBV-23, it was nearly sevenfold lower than expected. Thus, MACE and MI events in the Heplisav group occurred at rates similar to or below expected.

Secondly, I assessed the cardiovascular risk profiles of patients with reported acute myocardial infarction. This table summarizes baseline risk factors for cardiovascular disease for those who had MACE outcomes, contrasted with the total primary safety population stratified by randomized vaccine group shown on the right. Overall, cardiovascular risk factors were balanced between the two vaccine groups in the PSP.

MACE outcomes occurred in subjects in whom they would be expected to occur; on average, 10 years older than the overall cohort with about twice the prevalence of hypertension, diabetes, and hyperlipidemia. In fact, most subjects who had a myocardial infarction had two or more cardiovascular risk factors. While these data do not contribute to understanding

the imbalance in reported MI observed in HBV-23, it was reassuring to me that MACE outcomes occurred in patients expected to have them.

In my blinded review of clinical summaries and catheterization results for each reported acute MI event, I found that all cases had typical presentations for acute myocardial infarction described, and with cath data available for all but one of the cases, almost every case had a typical culprit lesion described and, for most cases, in the context of advanced multi-vessel obstructive coronary artery disease. I found no evidence of inflammatory or immune etiologies from review of the clinical annotations or cath reports. Importantly, there was no evidence for vasculitis, other immune-mediated vasculitides, or myocarditis.

Finally, I found no evidence of atypical or Type II myocardial infarctions, which are MIs caused by myocardial supply/demand mismatch, as may be seen with sepsis, with shock, hypertensive emergency, decompensated heart failure, and other such conditions.

To optimize sensitivity of potential MI events captured in MedDRA Standardized Medical Query process, or SMQ, was applied to the dataset. SMQs are validated predetermined sets of MedDRA terms intended to describe the same event and pathology with the established SMQs for MI applied. A similar process was used to identify potential nonfatal stroke events.

By the SMQ process for myocardial infarction, 25 subjects were identified in the primary safety population mapping to the five preferred terms highlighted here. Represented on this slide are the 22 preferred terms comprising the narrow SMQ for MI. Applying the broad SMQ for MI yielded no additional reported terms.

In the PSP, using the MI SMQ, 0.22% of Heplisav-B subjects and 0.1% of Engerix-B subjects had at least one preferred term reported. The only imbalance was in the preferred term "acute myocardial infarction." Reported preferred terms indicative of an MI, other than acute myocardial infarction, were similar between the two vaccine groups.

Next, the standard method for testing atherosclerotic cardiovascular disease outcomes was applied, which is routinely used in contemporary cardiovascular outcomes trials, capturing the spectrum of atherosclerotic cardiovascular events. This entails analysis of the composite MACE outcome of 3-point MACE, comprising time to the first event of death due to cardiovascular cause, nonfatal myocardial infarction, or nonfatal stroke.

The next step was central, blinded adjudication of all potential MACE outcomes that was performed by C5Research at the Cleveland Clinic, a global leader in the conduct of cardiovascular outcomes trials.

For cardiovascular event adjudication, all potential

events are identified across the PSP dataset using the SMQ process for nonfatal myocardial infarction and for nonfatal stroke, as well as all death events were submitted for review.

C5Research adjudicated all outcomes using event definitions and processes standard in contemporary cardiovascular outcomes research.

Although the Heplisav trials were not dedicated cardiovascular trials, I found it remarkable that for 18 of the 21 reported nonfatal MIs identified by the SMQ process, cardiac biomarker data were available. And for all but one of the reported acute myocardial infarction cases, cardiac catheterization data were also available. These data coupled with remarkably complete clinical annotations for all MI events allowed for meaningful adjudication of the potential acute myocardial infarctions. Let's look at the results.

This slide presents the cardiovascular events confirmed by adjudication; 0.33% of subjects in the Heplisav group and 0.21% of subjects in the Engerix group had adjudication-confirmed MACE outcomes. The incidence of cardiovascular death and nonfatal stroke were similar between the vaccine groups. The difference between the groups was only seen in myocardial infarction, where the 0.12% absolute difference accounts for the entirety of the difference in 3-point MACE.

If the difference in myocardial infarction observed in HBV-23 was caused by Heplisav, one would expect to see

differences across the spectrum of atherosclerotic cardiovascular disease outcomes, such as cardiovascular death and stroke, which is not the case here. Analyses of the composite and of the component outcomes each yielded 95% confidence intervals that spans unity.

Next, I was interested in evaluating the temporal associations between vaccine administration and the occurrence of cardiovascular events. This epi plot shows the timing of occurrence of MACE outcomes in the PSP, presented as incidence per thousand subjects to account for the 2.4:1 subject allocation ratio. The triangles along the horizontal axis reflect timing of vaccine administration. MACE outcomes occurred over the entire duration of the trials without clear evidence of clustering of events and, most notably, occurring without relation to the timing of the vaccine administrations. Importantly, events in the Heplisav and Engerix groups were similar between the groups in frequency shortly after each vaccine administration.

Now, with the same format, the timing of occurrence of myocardial infarctions is plotted, again presented as incidence per thousand subjects. MIs were scattered over the duration of the trials with no evidence for clustering of events immediately following vaccine administrations. Almost one-third of the reported MIs in the Heplisav group, that is, 5 of 16 events, occurred more than 300 days following the last

vaccine administration.

Here are the Kaplan-Meier curves of MACE outcomes by randomized group using a full scale on the vertical axis. The superimposed effectively flat lines at the top demonstrate the very small proportion of subjects who had MACE outcomes.

If Heplisav were to be associated with cardiovascular events mechanistically, it would most likely be due to it mimicking an acute infection such as influenza or pneumonia, which are known to increase the risk of myocardial infarction and stroke during and immediately following infection. The risk is highest in the first few days up to 2 weeks following the diagnosis of flu or pneumonia and, according to several studies, returns to baseline by 28 days.

Let me now magnify this figure to show more detail of these curves. Note now that the vertical axis starts at 0.994 instead zero. From the beginning of the trials through 28 days after the second vaccine injection, the Heplisav and Engerix cardiovascular event curves overlapped.

One large retrospective study suggests that a small incremental risk for cardiovascular outcomes after acute infection may last through 3 months after the diagnosis. In the Heplisav trials, Day 120 represents 3 months from the last Heplisav dose. The imbalance of MACE outcomes only begins to emerge at study Day 100 and beyond, with events occurring well beyond Day 300 in both groups.

Finally, I considered a series of possible vaccine-induced causes of MIs or MACE outcomes, finding no evidence or support for any of them. There was no imbalance in events shortly after vaccine administration, as would have been expected if 1018 mimicked an acute infection during the period of greatest reactogenicity.

Cardiac catheterization data, available for all but one of the patients with MI, provided no evidence of vasculitis or other immune-related vasculitides or myocarditis as potential causes of the events.

Finally, there was no evidence of a hypercoagulable state, conditions more commonly associated with stroke instead of MI, and typically with venous thrombotic events occurring more commonly than arterial. In the present dataset, venous and arterial thrombotic events, other than MI in one trial only, were uncommon, and they were balanced between the randomized groups. In addition, the laboratory sub-study in HBV-23 showed that Heplisav did not induce antibodies associated with immune-mediated hypercoagulability.

In conclusion, I conducted a thorough investigation of cardiovascular events observed in the Heplisav trials program, and I am unable to identify a plausible explanation for the imbalance in acute MI observed in HBV-23. Cardiovascular events occurred at or below expected rates in patients with cardiovascular risk. Clinical reports and cath data represent

typical MI events with no evidence for immune mediation. The lack of a close temporal association with vaccine administration, the lack of consistency across trials, and the lack of coherence across other atherosclerotic and thrombotic complications argue against causality.

Thus, my conclusion is the imbalance is most likely due to random variation in the context of a very small number of subjects having reported events and the Sponsor analyzing more than 1,400 adverse event terms, an exercise guaranteed to discover random imbalances. Nonetheless, the Sponsor has committed to conduct a postmarketing study to more definitively exclude any cardiovascular risk with Heplisav.

Thank you.

Dr. Janssen.

DR. EDWARDS: Thank you.

Questions for Dr. McGuire? Yes, Dr. Packer.

DR. PACKER: First of all, I'd like to apologize to all the members of the Committee. My questions are going to refer to terms that are used so commonly in cardiovascular clinical trials, and I'll -- what I'm going to try to do is make sure that I don't use acronyms because the acronyms are not going to make any sense to you. It makes sense to us, but it won't make sense to you. So I am making a promise, I am not going to use an acronym to the best of my ability.

DR. EDWARDS: Thank you.

DR. PACKER: First of all, let me just say that if there were a problem with an increase in the risk of myocardial infarction, you would expect it to occur in patients who are already at risk of a myocardial infarction. So a good way not to find an increase in risk of myocardial infarction is to vaccinate 20-year-olds because they don't get the disease and therefore you can't see a difference in the disease. So the only time when you can see differences in risk is if you study patients at risk. And so the fact that all of the patients here were -- had already major risk factors for myocardial infarction makes a lot of sense because those are the patients where you would see an imbalance, and Darren said that during his presentation.

It's also very hard, in cardiovascular disease, to determine whether an observed event rate is expected or not. There are so many factors, and the Sponsor has tried to say, well, based on age and gender and race, we would expect this many number of events, and the problem is that those models are very imprecise. There are lots of factors that don't go into the models. If those models were reliable, we would use them all the time. We never use them, and that's why we do randomized trials.

If those models were reliable, one would conclude that the current hepatitis vaccine reduces the risk of myocardial infarction by 80%, and I'm sure it doesn't do that. Well,

actually, I'm not sure.

(Laughter.)

DR. PACKER: There's also one other point which I think is worth mentioning, which is the term "MACE" may sound -- it may sound unfamiliar, and it should. Anyone who thinks the term is terribly sophisticated, please understand it was invented by cardiologists, and we are not sophisticated. MACE just stands for major adverse cardiovascular events. I wish we had a complicated term in there; we don't.

It is a collection of three events, in general: cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. They are collected that way because they are -- they can be ranked pathophysiologically under certain circumstances. For example, hypertension would increase all three. A platelet problem or decreasing platelet function would affect the frequency of all three.

But there are many examples where a problem occurs in only one, and if a problem occurs in only one, like myocardial infarction, it's really difficult to use MACE. MACE would have a dilutional effect if the problem were only in one of the three factors.

So what I want to do is really concentrate on myocardial infarction. The Sponsor has done a very nice job focusing on myocardial infarction, trying to identify myocardial infarction, adjudicating myocardial infarction. It sounds like

the data supporting the occurrence of myocardial infarction events was reasonably high quality and one could actually do a good job, which is amazing.

But, Darren, I have a question. Do you have a Kaplan-Meier curve of just MI and fatal and nonfatal MI for Study 23? Because what you showed was a Kaplan-Meier curve of MACE across all three trials.

DR. McGUIRE: Yes, we have -- do we have a slide just for HBV-23? We do have the slide for MI for the PSP in Kaplan-Meier. That may be a first start, and perhaps if we don't have it, we can get, after the break, the HBV-23 specifically. Can we see the MI Kaplan-Meier? We have to toggle between our presentation screen. Okay. So we don't have that ready to show. We will get that for you after the break.

DR. PACKER: Maybe I can just ask a question. Could you put up Slide CO-106 again? And I only ask for this because, in the absence of a slide of just myocardial infarction just in trial 23, this is the closest we had at the moment, and we'll get more.

DR. McGUIRE: Maybe the epi curve -- it gets to the timing of the epi curve-in from the core of the MI alone from HBV-23.

DR. PACKER: That would be great.

DR. McGUIRE: It shows also the timing of the MI curves, not in Kaplan-Meier format. There we go.

DR. PACKER: All right.

DR. McGUIRE: So these are the --

DR. PACKER: No, no. No, no. I don't want to see this.

DR. McGUIRE: Okay, go back to the Kaplan-Meier --

DR. PACKER: And here's the reason I don't want to see this, not because it isn't pretty; it's very nice. What I am looking at here and trying to understand, when you see a Kaplan-Meier curve, a clinical trialist immediately looks at one thing on a Kaplan-Meier curve, and we look at the denominators at the bottom because the denominators represent the number of people who had an assessment at any given point in time, the number of people at risk.

So what we see here is, in the first 100 days, a loss of about -- of information on about 200 patients in the Heplisav group and about 60 patients in the Engerix group. What happened here? I mean, why are these people lost to follow-up?

DR. JANSSEN: We don't have information on why people were lost to follow-up. There were a number of people who were lost to follow-up early in the trial.

DR. PACKER: So when you say there isn't an early risk of myocardial infarction, how do you know that if people with a myocardial infarction would be much more likely to be lost to follow-up?

DR. JANSSEN: We did look at lost to follow-up, and we have -- so we did look at the lost to follow-up subjects, and actually, the lost to follow-up subjects were younger, they had

lower cardiovascular risk factors. So this change on the left side is the not lost to follow-up; on the right side is the lost to follow-up.

Now, this is lost to follow-up over the entire duration of the trial. In both groups it was about 5%. And as you look at this, the people who are lost to follow-up on the right had fewer -- lower rates of cardiovascular risk factors than those on the left.

DR. PACKER: I guess what I'm asking is if there were -- amongst the 200 patients who were lost to follow-up on active therapy, if there were two myocardial infarctions that you missed. And you can't tell whether you missed them or not because you didn't get the lost to follow-up; you can't project the number of myocardial infarctions by the risk factors. So what I'm trying to get at is how do you know what happened to about -- and that's why I'm asking specifically for Study 23. I'd like to know how many people were lost to follow-up in the first 100 days of Study 23.

DR. McGUIRE: Yeah, we do have that Kaplan-Meier curve for Study 23 for myocardial infarction. And recall here, this is from a 0.995 vertical axis, so highly expanded.

DR. PACKER: So this is the curve that basically is the cause of everyone's attention because this is the imbalance, this is the time course of the imbalance. By the way, when we see curves like this, in general, we say that there is no time

dependency; that is, that the risk begins at Day 0. There's about 100 patients who are missing in the Heplisav group and 50 in the Engerix group, 150 patients with no MI information.

DR. McGUIRE: Right. Fair comment. It's 150 patients in a population, and I realize we cannot say anything about whether they had MI or not. I think somewhat reassuring is it's perfectly balanced between the two groups, suggesting that this is missing at random data, not -- can't convince you of that. But in an overall cohort with a 0.2% incidence of myocardial infarction, it would be difficult to understand how many events might have occurred in those 150 who are balanced between the two groups.

DR. PACKER: Maybe I'll ask the question this way, and please forgive me for asking the question this way. If there were two MIs that were present in the first 100 days in the Heplisav group that were not picked up, and none in the Engerix group, and that could happen just by a 2:1 randomization, then that -- then the split here would be 16:1 or 18:2, depending on whether you use adjudicated or non-adjudicated events. It's a small number of events, and it is so hard to interpret imbalances with a small number of events.

But, Darren, what number would get your attention? I'm asking because at 14:1, it is, you know, something that can't be dismissed. By the way, I would imagine 16:1 could be dismissed because of a sparse number of events. When do you

get an imbalance that you feel -- I'm sorry, it's small numbers, but it really makes me nervous. Is it 18:1 or --

DR. McGUIRE: I would say 14:1 makes me sufficiently nervous to agree with the Sponsor that this needs to be evaluated further, as will be proposed in the next presentation. There's a very robust proposal for subsequent assessment of cardiovascular risk in a very large patient population. So 14:1 gets everyone's attention.

I still believe, going through all of the background and the consistence, the coherence, I still believe it's most likely a play of chance or random variation, but not willing to make that final conclusion, and therefore, further evaluation is proposed.

DR. EDWARDS: Janet, did you have a question? Jack.

DR. BENNINK: Yes, just what made you take the assumption that this had to be like an acute infection or to, you know, base it on looking at it as if it needed to mimic an acute infection? What was that assumption based on?

DR. JANSSEN: Dr. Coffman, please.

DR. COFFMAN: Bob Coffman, Dynavax.

We certainly spent a lot of time thinking about what might possibly account -- be the basis for a causal relationship between this vaccine and acute myocardial infarctions, and surveying the literature, by far, the most plausible hypothesis would be that it did something similar to an acute infection

because, of course, one of the things that any acute infection will deliver is a signal through one of the nucleic acid-recognizing toll-like receptors. Toll 7 or toll 9, most likely.

And these two have a pretty clear set of predictions in terms of particularly the temporal association and the association with increased risk of both myocardial infarction and stroke, given, as Darren said, the common etiology of the two. So that seemed like the most plausible and, I think, the lack of temporal association is the strongest argument we have, certainly, that that's not the case.

There's really no significant suspicion that the toll 9-mediated events play a role in infection-driven myocardial infarctions. Again, toll 2 and toll 4 have been more implicated. However, it's unclear what exactly the driving mechanisms behind that are.

DR. BENNINK: But I sort of agree that it's certainly controversial, if not more than that. But I think you guys pointed out, even in your booklet here, what you gave as things, that there have been some studies in mice. I don't think that's necessarily a good model, and I think those studies have been, on both sides, either causing some or being a negative factor as well. So it's kind of gone both ways. I think those studies are clearly controversial in terms of whether TLR9 has any role at all in it, and it's a bad model, I

think, in the first place.

DR. COFFMAN: I think the studies you're referring to are those in terms of models of spontaneous atherosclerosis, what drives that. Again, TLR2 and TLR4 implication in the mouse ApoE model is very clear, that they're driving forces. TLR9 is low dose, and it seems to be protective at high doses.

Extremely high repeated doses could exacerbate, but that's -- in our evaluation, the notion that Heplisav, two doses of Heplisav would significantly promote what's really a long and chronic inflammatory process of atherosclerosis and increased MI frequencies in the time frame that we're looking at seem very unlikely. So although it's a possibility as well, it's less significant. The other possible etiology would be autoimmune, and I think that's been discussed. We've looked at all of the potential autoimmune causes that could be related to myocardial infarction and could be more consistent with the Kaplan-Meier curve that you just saw. And I think the evidence against those is reasonably substantial. As we all know, no vasculitis, no evidence of any phospholipid syndrome or any other autoimmune triggers of acute thrombosis and plaque destabilization.

DR. BENNINK: Yeah, but I think there was -- there is some aspect in terms of inflammatory aspects of atherosclerosis. In terms of M1 macrophages and inflammation, pro-inflammatory M1 macrophages play a role, I think, to some extent in plaques as

well.

DR. McGUIRE: And if I might add some clinical context. So there are two different issues here for coronary disease. One is the development and progression of atherosclerosis that I think the animal models may address. But I think what we're seeing here is destabilization of prevalent disease, and those with obstructive coronary disease are at risk for it. In days, weeks, and months, it would be prohibitively unlikely to develop clinically relevant atherosclerosis at this level.

And getting back to Dr. Packer's earlier comment, when we see myocardial infarction, this represents the destabilization of existing disease as opposed to progression. That's also indirectly reflected in the absence of acute revascularization in the Heplisav program. That happened in response to -- an MI or acute coronary syndrome revascularization only happened in one patient in each arm. It's not a progression of atherosclerosis phenomenon. It's destabilization of the existing disease. That's what points us directly back to Dr. Packer's point. As cardiologists, we go immediately, is there an inflammatory impulse or is there a procoagulant, hypercoagulable state?

DR. EDWARDS: Dr. Lee and then Dr. Packer.

DR. LEE: Thank you for showing us the Kaplan-Meier curve of the acute MI for Study 23. I wonder whether you have the similar Kaplan-Meier curve, but it was integrated, including

Study 16 and 10 and whether --

DR. McGUIRE: So do we have a Kaplan-Meier for MI in the PSP? This is the PSP. To confirm, this is PSP, right? Yeah, the numbers show it. Okay, so this is the K-M curve you're asking for. So this is HBV-10, 16, and 23.

DR. LEE: For acute MI or this is all --

DR. McGUIRE: Yes, these are the acute MIs.

DR. PACKER: I'm sorry, Darren, what's a serious myocardial infarction as opposed to a non-serious one?

(Laughter.)

DR. PACKER: I've never seen the word "serious" in front of myocardial infarction.

DR. McGUIRE: Right, it's combined -- it was coded as a serious adverse event.

DR. PACKER: Oh.

DR. McGUIRE: I agree with you, all MIs are serious.

DR. EDWARDS: Thank you.

Dr. Packer.

DR. PACKER: There is one thing that, Darren, it would be interesting to think about. The question is to what degree is the time course either reassuring or not reassuring? If you think that there should be -- if there's a post-inflammatory event, one could easily imagine that there should be front-loading of the event on the Kaplan-Meier curve. But there are chronic inflammatory diseases, rheumatoid arthritis for

example, where there is ongoing inflammation and an ongoing increased risk of myocardial infarction. There's also a trial that the results of which have just been announced and will soon be presented, where a sponsor used an interleukin-1b antagonist and found -- and suppressed interleukin for about 9 months but found a continuing divergence of the curves. The interleukin-1b antagonist decreased the risk of myocardial infarction and similar events, reportedly.

Is it not possible that whatever sets up the immune response for hepatitis sets up an ongoing factor that could resemble that of rheumatoid arthritis in patients with atherosclerotic disease?

DR. McGUIRE: I think that's perfectly possible that patients immunized with a new vaccine may have a constitutive inflammatory state that's not otherwise present. But if that were the case, I would fully expect a pulsatility of the risk signal immediately following in the periods of highest reactogenicity. And we also -- I'll refer to Dr. Janssen. There are, as imperfect as they are, CRP data available with this vaccine versus comparator.

DR. PACKER: The only problem with feeling really comfortable about the lack of the initial pulse is the missingness of data. If there were a pulse of myocardial infarctions -- I'll just make up a number, five myocardial infarctions, and they didn't come back for follow-up because

that's what people with myocardial infarctions do, they don't come back for follow-up, how do you know there isn't an initial pulse?

DR. JANSSEN: So we did look at lost to follow-up. So, as you know, the people in the trial who had MIs were the people who had cardiovascular risk factors. So we looked at the cardiovascular risk factors in the lost to follow-up group, and what you see, this is Engerix divided by Heplisav, is that if there's any additional cardiovascular risk factor, it was in the Engerix group, not in the --

DR. PACKER: No, no. No, no. No. You can't make a prediction of how many myocardial infarctions you missed by looking at the risk factors in that group. You can't do that. So my question is how do you know that there is not an initial pulse if you have missing data in more than 100 people?

DR. McGUIRE: The short answer is there's no way to know. The reassurance is there's not an extreme imbalance in the background risk factors, as is shown here. It's perfectly balanced between the two groups in the 2:1 allocation sequence, 100 versus 50, early on. But at the end of the day, one or two or three events would really materially change the ratios, and I fully understand that. So there's no way to know. They're still small numbers and it's still post hoc, but it's something that is lingering, which leads to the requirement for further evaluation in the postmarketing study you'll hear about.

DR. PACKER: Yeah. I mean, there is no -- there's no solution here. It's just that if you were missing three or four events, it would actually look like a pulse, and you could easily be missing three or four events if you're missing data on 100 people.

DR. McGUIRE: In that case, I'd blow the vertical axis back up to 1.0.

DR. PACKER: Oh, okay.

DR. McGUIRE: The trouble here we get, we're really singling in very small numbers of events, and I agree fully, we can't be certain what happened with the 150 missing early.

DR. PACKER: You don't know. Right.

DR. JANSSEN: I think it's important to note that in HBV-23 there were 15 acute myocardial infarctions in a 2:1 randomization. If we saw them distributed in the 2:1, it would've been 10:5. So three or four in either group.

DR. PACKER: Let me say that, of course, it's 2:1, and so it's not a 14:1 risk; it's a 7:1 risk. Is that okay?

DR. JANSSEN: Well, as you said, it could be three. The difference is three or four events. So instead of 10:5, you'd see 14:1.

DR. PACKER: Yeah, okay, the difference is three or four events in a trial. The difference would be much more substantial if it were given to millions of people.

DR. JANSSEN: As Darren had said, we don't think there's

an increased risk with this, and largely, we think the temporality is the strongest. You had a comment about setting -- about initiating a chronic inflammatory response, and I'd like to ask Dr. Coffman to comment on the duration of the effect of 1018 on the immune system.

DR. COFFMAN: Bob Coffman, Dynavax.

Yes. I mean, we certainly have a good deal of data in terms of measurable biological responses to 1018 after Heplisav administration as well as -- and this gets to data from many other studies with similar CpG oligonucleotides. Can I have CO -- OB-6, I think it is? There. Let me just show you a particularly good example, and this is actually done with patients that received Heplisav. And what we're monitoring here are three panels of interferon-regulated genes, well-characterized interferon-regulated genes, and this is monitoring the magnitude of induction.

And this is a reflection based -- although you're measuring this in peripheral blood, what you're measuring is the interferon that's produced locally at the injection site in a draining lymph node, and this shows that the peak is at Day 1. Afterwards, there's a several-fold increase in these three-gene sets. It decreases, although still a bit elevated at Day 3; returns to baseline in Day 7. We've seen this in clinical studies repeatedly with multiple ones. And this is one way of looking at it.

But the short answer is we've really seen no evidence, in any of our clinical studies, that CpG has longer-lasting effects than this. I think the consistent view of CpGs is -- it's kind of a hit-and-run mechanism.

DR. PACKER: Please understand, you know, I'm not suggesting that I or anyone else knows whether this imbalance is real. I don't think that's knowable.

DR. COFFMAN: Right, right.

DR. PACKER: All I'm trying to do is find out what information you have given me that I can rely on. One thing, just to make sure, I can't rely on the projected rates because you can't do that. I can't rely on the absence of an initial pulse because you have the lost to follow-up at the beginning. I can't rely on MACE. I want to look at myocardial infarction per se.

So what I can rely on is an observation of a 14:1 to split or a 16:2 split in a randomized trial, and that is what I can rely on. How I interpret that is -- you know, leaves a great deal of uncertainty, and I think everyone would agree with that.

DR. EDWARDS: Dr. Ward.

DR. WARD: You mentioned early on that other vaccines involve this pathway, I think. So I was wondering if there are any cardiovascular data for those other vaccines or if there has been any myocardial events associated with those vaccines.

DR. JANSSEN: Nothing, no.

DR. EDWARDS: Okay, I think we should go ahead, then, to the last segment of this presentation, the benefit-risk conclusion, by Dr. Poland.

DR. JANSSEN: No, postmarketing.

DR. EDWARDS: Postmarking plan, yes. Sorry. Thank you.

DR. JANSSEN: Thank you, Dr. McGuire.

Now I'm going to talk about our postmarketing plans and I'll summarize the safety findings.

So we believe a postmarketing surveillance study is the most feasible and appropriate step now to confirm the safety of Heplisav. Based on ongoing communication with FDA, this represents our most current proposal for postmarketing. It will be done by Kaiser Permanente in Northern and Southern California regions, and this has been updated from what you saw in our briefing book.

We're proposing to evaluate 40,000 vaccine recipients, 20,000 of whom receive Heplisav compared with 20,000 who receive another hepatitis B vaccine. Now, it's anticipated conservatively that the entire 40,000 patients will accrue within 1 year. Data will be collected through 13 months after the first dose of vaccine.

Now, in this retrospective electronic medical record analysis, we'll specifically analyze MACE and immune-mediated events. And, in addition, we'll assess herpes zoster and

anaphylaxis.

Now, an independent data monitoring committee will review the interim findings from analyses at 12 months and 18 months, to ensure that no major adverse safety differences are emerging.

Now, for the comparison analysis, a sample size of 20,000 subjects per group will provide greater than 99% power to rule out a twofold increase in the risk of MACE, if the background incidence rate is 6 per 1,000 person-years.

Based on the projected incidence of acute myocardial infarction in the Kaiser populations, we estimate we should be able to rule out the relative risk observed in HBV-23 in the data analysis at 12 months after study start.

The proposed sample size of the postmarketing study has 87% power to detect an increased risk greater than or equal to 2.5 for an event assuming a background incidence of 1 per 1,000 for an immune-mediated event.

Now, let me summarize the safety of Heplisav. The safety data presented today, in more than 13,000 adults, show that Heplisav is well tolerated and with an overall similar safety profile to the existing hepatitis B vaccine. Rates of post-injection reaction, adverse events, and medically attended adverse events were largely balanced between the Heplisav and Engerix groups.

The overall serious adverse event rate was similar for the

two arms, with imbalances in individual terms in both directions including acute MI for Heplisav and prostate cancer for Engerix.

The small apparent numerical imbalance in deaths was largely driven by accidental drug overdose, the only single cause of death that was imbalanced. Importantly, deaths due to cardiovascular cause were balanced.

HBV-23 was conducted because VRBPAC and the FDA determined that the size of the previous Heplisav safety database was too small to detect uncommon immune-mediated events. The trial was conducted in part to better understand the potential relationship of Heplisav to GPA and THS. Even though HBV-23 was as large as the previous two trials combined, neither event was observed.

Comprehensive analyses of all new-onset immune-mediated events in the new Phase 3 safety database showed rates to be balanced with Engerix. While more individual events occurred in the Heplisav group, there was diversity of immune mechanisms with no common pathway. Autoantibody conversions were balanced, except for one transient elevation in a nonspecific anti-phospholipid antibody that has no clear clinical significance.

A careful and thorough evaluation found that MIs occurred in people in whom they'd be expected with no temporal relationship to vaccination and at rates with the limitations

that were similar to or lower than expected and, importantly, with no evidence for immune etiologies.

Now, admittedly, we struggled to find a coherent pathophysiologic explanation for the numerical imbalances we've identified. We think it's unlikely that stimulating a single pattern recognition receptor, as 1018 does, could cause this wide diversity of events.

We'll conduct a postmarketing surveillance study to analyze MACE and immune-mediated events, in particular, to confirm the safety of Heplisav.

I'll invite Dr. Poland now to present the benefit-risk assessment. Although if you've got questions for postmarketing, I won't, then.

DR. EDWARDS: Any questions about postmarketing? And I think it's clear we will be foregoing our break. So if there are any immediate biologic needs that you have, you'll just have to get up and go.

Yes, Mark.

DR. SAWYER: So I think it's clear we're all going to be very interested in the results of this postmarketing study. I'm curious about the projection that Kaiser can find 40,000 people to immunize in a year.

Could you characterize more what that population is going to be? Are they people who already have an indication for hepatitis B vaccine? Because Kaiser is generally pretty good

about immunizing their population who have an indication, and so I would suspect a lot of them already are diabetics, for example.

DR. JANSSEN: This is based on data from Kaiser for the last several years. These results are actually conservative based on the number of adults they vaccinate every year. They also have been -- and I can't comment further. There's an abstract that's going to be presented at an upcoming meeting. They have been trying to increase their rates. Southern California has been trying to increase the rates of vaccination in people with diabetes. Northern California has not been doing that yet.

DR. SAWYER: And will this be all age groups of 18 and above or is it --

DR. JANSSEN: Yes. Yeah. Yeah, and they vaccinate people 18 to 79, actually, based on their data from the last several years.

DR. EDWARDS: Dr. Kotloff.

DR. KOTLOFF: I'm wondering, with regards to age, you know, if this is very skewed to younger people who are travelers, for example. Then you may not be powered to examine the occurrence of the event in the people at risk. I'm wondering if --

DR. JANSSEN: That's certainly something we're going to be looking at. As I had mentioned, they vaccinate people from 18

to 79, and it actually, surprisingly to me, is the decade, age decades, deciles that actually have the highest rates of vaccination are in the 40s and 50s.

So the other thing is Kaiser Northern California has been talking about implementing a system to increase vaccination rates in diabetics. So it's possible, also, that we'll see a lot more people with diabetes being vaccinated during that period of time as well.

DR. EDWARDS: Any other questions? Yes, Dr. Packer.

Or no, you had a follow-up on that?

DR. KOTLOFF: It's kind of stepping back a bit, but I was wondering, somebody mentioned CRP, and I was wondering if we could know what those data were.

DR. JANSSEN: Yeah. Could we have the CRP slide? We did CRP in HBV-10, and what we saw was -- it's a little complicated. If you look at baseline, if you look at the normal at baseline and then look at high for Visit 5, which is 4 weeks and Visit 7 is 8 weeks -- it's 12 weeks, actually, and this is -- as you can see in the Heplisav group, at Visit 5 it was 7% had high CRPs compared to 10% in the Engerix group, and then at 12 weeks it was 9 compared to basically 9. So we didn't see any evidence of a difference in CRP.

DR. EDWARDS: Dr. Packer.

DR. PACKER: Yeah. By the way, a cardiologist would never show CRP data that way. Just so you know. We have no idea

what a normal CRP is, from a cardiovascular risk point of view. Also, was that a high sensitivity assay or --

DR. JANSSEN: I will have to get back to you about that.

DR. PACKER: Ignore the question. So let me just ask a question. Have you considered doing your observational study in a way which is event driven?

DR. JANSSEN: Yes, absolutely. I think that's an important way to look at it because we share the same concern. Are we going to -- are enough people at risk --

DR. PACKER: Sure.

DR. JANSSEN: -- going to be vaccinated to answer the question. Now, obviously, we won't develop the protocol until after approval, but that's certainly something we're thinking about, is making it event driven.

DR. PACKER: Sure. Could you at some time come up with the total number of MIs you think that you ought to be targeting in a postmarketing study? In other words, if you're going to make it event driven, what's the total number of myocardial infarctions, not MACE events, the total number of myocardial infarctions you would like to target?

DR. JANSSEN: Yeah. I'll have to get back to you on that after the break, the number of myocardial infarctions that we would want in an event-driven postmarketing study. For MACE, it's about 85.

Oh, Darren?

DR. McGUIRE: If I may just address that. Sorry, that's really fine. So Darren McGuire, UT Southwestern.

So whatever event you're measuring, as you know, Professor Packer, the number is fixed. So if we want to just focus on MI, or the Sponsor does, I haven't been involved in the postmarketing planning, the number is 87, if you want to exclude upper confidence limit of 2.0, if we find that's acceptable. That's assuming. And just to be clear, we're not talking about accepting a twofold increased risk. That's the exclusion of the upper confidence limit predicated on a point estimate of 1.0 or less.

So this is a design for a standard non-inferiority assessment for neutrality of the compound, or the experimental, and it takes 87 events to exclude 2.0 by FDA standard. If we want to go to exclude 1.8, that's 122 events; 1.3, 622 events. It doesn't matter what you're measuring, the number of events will drive it. And I agree completely that it has to be event driven, at least a part of the design, to have a minimum number of events for statistical precision.

DR. PACKER: Yeah. Darren, by the way, I don't think there's a magic number of events. The more the number of events, the greater your confidence is that you don't have something. I would just say that it would be important to do it event driven than based primarily on MI because that's where the signal is.

And by the way, any incremental information is better than what you have now, which is a sparse number of events with, you know, a worrisome imbalance.

DR. EDWARDS: Jack.

DR. BENNINK: Yeah. In terms of postmarketing or any of this, did you consider doing a study that's more focused on cardiac risk patients and, you know, with multiple -- maybe more than one cardiac risk, two or three, whatever it is? And then noninvasively kind of following them even before and during this thing for a year or whatever to try and, you know, image them, whatever the case is, to see if you can't, you know, almost see if there is a problem in terms of that and comparing it with -- it doesn't even have to -- it wouldn't even have to be an Engerix sort of thing. It could be just a randomized study with comparable patients with comparable cardiac risk and age and all of these other factors that you have. Did you consider that at all?

DR. JANSSEN: I'd like to ask Dr. McGuire to comment on that.

DR. McGUIRE: Darren McGuire, UT Southwestern.

So I think, to the end of your question, you got to the point of considering a randomized comparison. The challenge with that is that requires randomized trial oversight, ethical review, informed consent provision. You know, we're talking about a trial of somewhere between 20- and 40,000 patients.

That's larger than -- even with the greatest efficiency in cardiovascular medicine, that's a tall order to get, and it would take 7 to 10 years probably to do that trial. That's the efficiency of the observational comparison.

If the product is being used on label as indicated, then it's an observational registry with a prospective plan for data collection. It does not require informed consent or enrollment into a clinical trial. We just would look at the outcomes of the patients who got one vaccine versus the other. So the efficiency of the rapidity is afforded in the -- specifically in the Kaiser system, and they've done these many other times for vaccines and also for therapeutics. I work in the diabetes and heart disease world, and Kaiser's done this postmarketing, large numbers, rapidly enrolled to get to the bottom of the -- get to the answer rapidly. It would take us, in a clinical trials domain, at least a decade to get to the conclusion.

DR. EDWARDS: Okay, so let's go ahead, then, with the benefit-risk conclusion by Dr. Poland, Professor of Medicine, Director of the Vaccine Research Group at Mayo Clinic.

DR. POLAND: Good morning. I'm Dr. Greg Poland. I'm Professor of Medicine and Infectious Diseases and Director of the Vaccine Research Group at the Mayo Clinic. I'd like to share my clinical perspective on the benefit-risk of Heplisav and why I believe that Heplisav provides me, as a clinician, with a critical tool that will lead to the protection of more

adults in the U.S.

By way of experience, I've been a practicing internist for 36 years. I've been the PI of roughly 40 vaccine clinical trials, involved in many more, and exposed to hundreds more as the Editor-in-Chief of the journal *Vaccine*. I was the chair of the safety evaluation and adjudication committee, or SEAC, for the HBV-16 and 23 trials. Unfortunately, I've also seen more cases of hepatitis B and its sequelae than I would have ever wanted to see in my career.

While the impressive success of the hepatitis B vaccine in children could create the perception that a new hepatitis B vaccine isn't needed, it's a far different story in adult medicine. Despite the availability of hepatitis B vaccines and longstanding recommendations for vaccine use, acute cases are increasing in adults.

Hepatitis can lead to liver failure, cirrhosis, and liver cancer. The importance of rapid, safe, and effective hepatitis B protection can't really be overstated.

Lastly, there are critical limitations with the currently licensed vaccines available for adults in the U.S., resulting in unpredictable and suboptimal protection. For me, as a clinician who's dedicated to protecting my patients against vaccine-preventable diseases, three critical needs are apparent:

Number 1, the rapid induction of immunity, a way of

protecting my patients as quickly as possible, particularly among higher-risk patients and healthcare workers.

Second, the reliable induction of immunity. I want to feel confident that when my patients get the vaccine, they'll be protected against this morbid disease.

Third, I need a vaccine with a reduced or shortened immunization schedule. And these vaccines, of course, must meet acceptable levels of safety.

Let me briefly review what I see as important data supporting each of these three points with the Heplisav-B vaccine.

First and most critical, Heplisav provides rapid induction of protective immunity. By addressing this critical challenge, Heplisav has the potential to protect more adults by inducing rapid and early immunity, almost 90% by 8 weeks and nearly all by 12-plus weeks.

As seen here, rates of seroprotection were higher, achieved earlier and more reliably with Heplisav compared to Engerix, which is especially important for those at high risk for HBV infection and for those who are in contact with them, such as healthcare providers.

Secondly, the reliable induction of immunity is critical to both patient and physician. As the data show, Heplisav consistently and reliably results in significantly higher seroprotection rates across diabetes status, age range, obesity

status, smoking status, and gender compared to the current standard of care.

As a clinician wanting to protect my patients, I note that almost 92% of subjects 60 to 70 years of age developed immunity with Heplisav, comparable to the seroprotection rate observed in much younger 18- to 39-year-old subjects who received Engerix-B.

And since the third dose of current hepatitis B vaccines is required for seroprotection in most younger adults and nearly all older adults, they remain at risk for hepatitis B for a prolonged period of time between that second and third dose. This is a concern for those at imminent risk of infection, such as healthcare providers, emergency first responders, and travelers to high-prevalence countries.

Common sense suggests that patients are much more likely to complete a 2-dose/1-month schedule versus a 3-dose/6-month schedule.

The model benefit of the two-dose versus a three-dose schedule using measured adherence at an STD clinic with MSMs demonstrated a 29% higher seroprotection rate for the two-dose regimen of Heplisav compared to a three-dose vaccine. Thus, a shorter immunization schedule may actually increase true protection.

A model published by the CDC was used to estimate the public health benefit in adults with diabetes less than 60

years of age, an at-risk group in which CDC recommends routine vaccination.

Using this model, we can see that when extrapolating to five million unvaccinated people with diabetes, which represents half of the unvaccinated adult population with diabetes under the age of 60, Heplisav would prevent an additional 29,000 estimated infections and the significant complications of HBV over their lifetimes.

Or better said, in this model, using Heplisav leads to an additional 29,000 individuals whose lives will not be interrupted by hepatitis B. This is a 72% decrease in hepatitis B-related outcomes compared to Engerix-B.

From my perspective, the safety profile of Heplisav is similar to Engerix, which is reassuring.

The results from the clinical trial showed similar rates of local and systemic post-injection reactions, adverse events, and serious adverse events. Similar rates of deaths were observed when excluding drug overdose. Similar rates of new-onset immune-mediated disease and autoantibodies were observed between Heplisav- and Engerix-treated subjects.

In regard to the imbalance seen in myocardial infarction, data from three Phase 3 trials involving over 13,000 total subjects showed a small numerical difference in proportion with the single preferred term of acute myocardial infarction in one of these three trials.

My own experiences as a PI and editor of *Vaccine* is that these sort of chance events, like the inexplicable difference in prostate cancer seen with Engerix, are commonly observed. It's simply the nature of probability. For acute myocardial infarction, Dr. McGuire's investigation is consistent with this interpretation. Nonetheless, we all know that rare events, coincidental or not, may occur with wider use, and therefore, I would certainly agree with and advocate for a careful postmarketing pharmacovigilant study as proposed.

I believe the data support that there will be substantial public health benefits with the use of Heplisav in adults.

As chair of the SEAC, I reviewed, with the other members of the SEAC, all possible new-onset immune-mediated adverse events. Although there were more of these events in the Heplisav-B group, several issues of note are apparent. First, the rare serious AESIs were balanced between arms. Second, no rare serious AESIs were observed in HBV-23. And thirdly, the AESIs constitute a group of small numbers of multiple diagnoses, representing multiple unrelated immunologic mechanisms of action. In the end, after unblinding of the clinical trial, the SEAC concluded there was no increased risk of any individual immune-mediated event.

In conclusion, Heplisav addresses an important public health need by providing higher seroprotection to more adults earlier with fewer doses in a shorter period of time. Heplisav

induced high rates of seroprotection in all adults, including populations with reduced immune response to the currently available vaccines. Heplisav provided earlier seroprotection that is beneficial to high-risk persons who need rapid protection. In addition, administration of Heplisav should increase adherence by virtue of a shorter two-dose schedule over 1 month, rather than a three-dose schedule over 6 months.

To refer back to the National Academy's recent report calling for the elimination of viral hepatitis, it's clear from the increasing risk in the surveillance data shown by Dr. Schaffner, if we're going to eliminate hepatitis B in the United States, we must improve our vaccine options for adults, for those most at risk.

As a former member of VRBPAC, I believe that the immunogenicity and the safety data are sufficient to support the licensure of Heplisav in all adult populations.

Thank you.

DR. EDWARDS: Are there any other pressing questions?

(No response.)

DR. EDWARDS: Okay, thank you. I'd like now to proceed to the FDA presentations. The first will be on immunogenicity by Dr. Alexandra Worobec, Clinical Reviewer in the Division of Vaccines and Other Related Product Applications.

DR. WOROBEC: Good morning. My name is Dr. Alexandra Worobec from the FDA. I will be presenting a summary of the

immunogenicity evaluation of Heplisav-B along with updates regarding this analysis.

Next slide, please. Or do I do it? Oh, I do it, okay. All right.

I would like to now present VRBPAC's conclusions regarding clinical immunogenicity from the 2012 Advisory Committee meeting followed by a summary of events that help provide a background for the immunogenicity data that I will be discussing today.

In 2012 VRBPAC voted 13 to 1 that data from Phase 3 studies HBV-10 and 16 were sufficient to support effectiveness.

The March 2016 Complete Response included revised clinical study reports for HBV-10 and -16 to address Applicant-identified errors in the immunogenicity analyses.

Revised primary immunogenicity analysis for HBV-10 and -16 will be presented and compared with the primary immunogenicity analysis in the original clinical study reports. We heard a little bit about HBV-23 this morning. I want to remind everyone that HBV-23 was designed and conducted to address VRBPAC's recommendations to acquire additional safety data for Heplisav-B. HBV-23 immunogenicity data were not needed to establish effectiveness, and these data will not be presented today.

The overall study designs for the two original Phase 3 studies conducted with Heplisav were similar. They were both

subject and observer-blind, randomized, active control studies. Three injections were given in each of these studies. In the Heplisav-B arm, injections were given IM at Weeks 0, 4 with placebo given at Week 24. And for Engerix-B, vaccinations were given IM at Weeks 0, 4, and 24.

The primary immunogenicity endpoint was defined as a difference in seroprotection rates. And the two studies differed in the timing of measurement of the SPR for the Engerix-B arm with SPRs measured at Week 28 or 4 weeks after the last dose for HBV-10 and measured at Week 32 or 8 weeks after the last dose for HBV-16. The SPR for the Heplisav-B arm used for determining the primary immunogenicity endpoint was measured at the same time point for Studies 10 and 16 and were measured at Week 12.

Success criteria for these studies were defined as a non-inferiority margin of 10% for the between group difference in SPRs. Non-inferiority was established if the lower two-sided 95% confidence interval limit around the Heplisav-B SPR minus the Engerix-B SPR was greater than -10%.

With regard to subject enrollment, Study 10 enrolled adults 18 to 55 years of age. They were randomized 3:1 to Heplisav-B or Engerix-B. A total of 2,415 subjects 18 years of age and older were enrolled, with 1,809 subjects enrolled in Heplisav-B arm and 606 subjects enrolled in Engerix-B arm.

I need to mention that Study 10 also randomized and

vaccinated 13 subjects who were younger than 18 years of age. They were 11 to 18 years old and are not included in the numbers and immunogenicity analyses presented.

Study HBV-16 enrolled adults 40 to 70 years of age. They were randomized 4:1 to Heplisav-B or Engerix-B. A total of 2,452 subjects were enrolled, with 1,969 subjects enrolled to the Heplisav-B arm and 483 subjects enrolled to the Engerix-B arm.

I will now summarize the immunogenicity results for Studies 10 and 16. Before I discuss the actual findings, I want to reiterate that the clinical study reports for Studies 10 and 16 were revised in 2016 to reflect revised subject accounting for the per-protocol populations for both of these studies. The change in the per-protocol population numbers were negligible.

Primary immunogenicity endpoints were recalculated for each study using the revised per-protocol populations, and the revised per-protocol population numbers resulted in a negligible change numerically in the primary immunogenicity endpoint and did not affect the non-inferiority comparison results with Engerix-B.

If we look at the SPRs in the 95% confidence interval for the difference in the SPRs for each study as shown in this table, for the original unrevised clinical study report in 2012 and 2016, they differ by very little numerically.

So, in summary, non-inferiority was demonstrated between Heplisav-B and Engerix-B for Studies HBV-10 and -16 for both immunogenicity analyses conducted in 2012 with the original per-protocol population and in 2016 with the revised per-protocol population.

So, in conclusion, Heplisav-B met pre-specified non-inferiority criteria for immunogenicity as compared to the licensed active comparator hepatitis B vaccine, Engerix-B, for the revised per-protocol population. Conclusions regarding immunogenicity of Heplisav-B based on the revised per-protocol population were unchanged. Immunogenicity of Heplisav-B was established in the two Phase 3 studies, HBV-10 and -16. Study HBV-23 was not needed for demonstration of effectiveness of Heplisav-B.

Okay, is that it? I think that's it.

DR. EDWARDS: Questions?

I have a question for the Committee. There appears to be some need for some to have a break. So if we have a break, then we will have to truncate the lunch because there's large numbers of public comment. So would you like to have a 10-minute break now and a shorter lunch, or would you like to plow ahead?

Okay, break now? Raise your hand.

(Show of hands.)

DR. EDWARDS: Okay, no break.

(Off microphone comment.)

DR. EDWARDS: So we have some lost to follow-up here.

(Laughter.)

DR. EDWARDS: Let's do it again.

Break now?

(Show of hands.)

DR. EDWARDS: No break. Okay.

We'll hear from Darcie Everett, Dr. Darcie Everett, who will present the safety data. She's also a clinical reviewer for the Division.

DR. EVERETT: Good morning, I'm Dr. Darcie Everett, Medical Officer in FDA. I'm responsible for the clinical review of the safety data Dynavax submitted in support of their BLA for Heplisav-B.

This is an outline of my presentation. I'll start with the background, which includes an overview of the clinical trials submitted to support licensure, and the regulatory history. I'll present a summary of the data that was previously presented to the VRBPAC in the November 2012 meeting. Then I'll present the safety data from the Phase 3 trial DV2-HBV-23.

Following this, I'll present the integrated analysis of safety for the three Phase 3 trials. I'll then summarize the safety findings, and finally, I'll present the pharmacovigilance plan proposed by Dynavax. For the remainder

of my presentation, I'll refer to the studies by simply their study number; for example, I'll refer to Study DV2-HBV-23 as Study 23.

So this slide is simply to remind you that Heplisav-B consists of 20 µg of recombinant hepatitis B surface antigen and 3,000 µg of a novel CpG adjuvant.

The proposed indication is for immunization against infection caused by all known subtypes of hepatitis B in adults 18 years of age and older. Heplisav-B is administered as a two-dose series of 0.5 mL administered 4 weeks apart.

This is a summary of the numbers of subjects in the safety populations for studies submitted in support of licensure. There were three pivotal trials, Studies 10, 16, and 23, with a total of 9,365 subjects who received at least one dose of Heplisav-B and 3,867 subjects who received at least one dose of Engerix-B.

There were two supportive trials using a final formulation dose and schedule. These were Studies 14 and 22, both of which were uncontrolled. These studies enrolled an additional 232 subjects who received at least one dose of Heplisav-B.

The Sponsor's total safety population includes an additional 441 Heplisav-B recipients and 333 Engerix-B recipients who were enrolled in studies but did not use the final formulation dose or schedule of Heplisav-B.

The FDA integrated analysis of safety will primarily focus

on the 9,365 subjects who received Heplisav-B in the Phase 3 clinical trials as the relevant safety information, as the other studies were either uncontrolled or used a different formulation dose or schedule.

Safety surveillance differed in the three Phase 3 clinical trials. Solicited adverse events were monitored for 7 days following each vaccination in Studies 10 and 16. Unsolicited adverse events were monitored for 28 weeks in Study 10 and for Study 16.

Solicited adverse reactions and unsolicited adverse events were not collected in Study 23, but medically attended adverse events, or MAEs, were collected for 56 weeks from the first dose in Study 23. MAEs were not specifically collected in Studies 10 and 16.

Serious adverse events were collected for 28 weeks in Study 10, for 52 weeks in Study 16, and for 56 weeks in Study 23.

Adverse events of special interest or potentially immune-mediated adverse events were monitored for 52 weeks in Study 16 and for 56 weeks in Study 23. They were not monitored in Study 10.

It is important to note that because Heplisav-B was given as a two-dose series and Engerix-B was given as a three-dose series, subjects who received Engerix-B were monitored for a shorter period of time following the last active dose.

However, for each study, subjects in Heplisav-B and Engerix-B groups were monitored for the same total period of time following the first dose.

Now I'm moving on to present a summary of data presented at the November 2012 VRBPAC.

This table shows the solicited adverse reaction frequencies reported by subjects in the 7 days following dose 1 and dose 2 in Heplisav-B, and dose 1, 2, and 3 of Engerix-B. All doses of both vaccines were well tolerated. There were slightly more injection site redness and swelling reported in the Heplisav-B group compared to the Engerix-B group following doses 1 and 2. In the first BLA review, this was considered to be not clinically significant, and solicited adverse events were not collected for Study 23.

In Studies 10 and 16, overall rates of unsolicited AEs were similar between treatment groups, and rates of SAEs were slightly lower in the Heplisav-B group compared to the Engerix-B group. There were no deaths reported in Study 10.

In Study 16, there were two deaths. A 46-year-old man with no past medical history who received Heplisav-B had a fatal pulmonary embolus at 7 weeks after dose 2. A 64-year-old man with a history of hypertension and gout who received Engerix-B had a fatal acute myocardial infarction within 7 weeks after dose 2. Neither death was assessed by the investigator as related.

Adverse events of special interest or events that are potentially immune-mediated were identified in both studies. These events will be discussed in more detail later in the presentation.

So before I move on to present additional clinical trials data, I want to talk a little bit about the regulatory history.

The data I just presented to you was presented in a VRBPAC meeting in November 2012. The members voted 13 to 1 that the immunogenicity data were adequate to support effectiveness. However, they voted 8 to 5 with 1 abstention that the available data were not adequate to support safety given the insufficient size of the safety database in the context of the novel adjuvant.

So that brings us to Study 23, which was performed following the 2012 VRBPAC to increase the size of the safety database.

Study 23 was an observer-blind, active-controlled, multicenter U.S. trial. Subjects were randomized 2:1 Heplisav-B to Engerix-B. The study enrolled adults 18 to 70 years old. Subjects were stratified by age into two age groups: 18 to 39 and 40 to 70 years. Subjects were also stratified by study site and diabetes status. The primary safety objective was to evaluate the overall safety of Heplisav-B with respect to clinically significant adverse events.

In Study 23, MAEs, SAEs, and AESIs were monitored for 56 weeks. AESIs were referred to a safety evaluation and adjudication committee, or SEAC, for review. A laboratory sub-study was also performed in which a subset of approximately 300 subjects had serum chemistry, hematology, urinalysis, clotting assessments, and thrombotic assessment at baseline and several post-vaccination time points.

The safety population was defined as subjects who received at least one study injection and had any on-study safety data. There were 8,368 subjects vaccinated, 5,587 of whom received Heplisav-B and 2,781 of whom received Engerix-B.

This table presents the demographic subgroups for subjects vaccinated in Study 23. These data suggest that randomization was adequate as there were no notable differences between the treatment groups.

This table shows selected baseline characteristics suggestive of increased cardiovascular risk in the two treatment groups. Overall, subjects in the Heplisav-B group and Engerix-B group were similar in terms of prevalence of cardiovascular risk factors at baseline.

All medically attended events, which include SAEs, were reported in approximately 46% of both treatment groups. There was a similar percentage of subjects in each treatment group that reported an MAE that was assessed as severe. The rates of subjects assessed as having an MAE that was related was low in

both treatment groups.

There were small imbalances between treatment groups noted in some MAEs. Using the criteria of MAEs that were reported in at least 0.5% of either treatment group and at least twice the frequency in one treatment group compared to the other, three MAEs were identified. Herpes zoster was reported in 0.7% of Heplisav-B recipients as compared to 0.3% of Engerix-B recipients. Tooth infection and exostosis were reported in a greater proportion of Engerix-B recipients as compared to Heplisav-B recipients.

Nonfatal serious adverse events were reported in 5.8% of Heplisav-B recipients and 5.1% of Engerix-B recipients.

There was an imbalance between treatment groups in events that are categorized in the Medical Dictionary for Regulatory Activities, or MedDRA, System Organ Class of cardiac disorders including nonfatal and fatal serious events: 0.9% of subjects in the Heplisav-B group and 0.5% of subjects in the Engerix-B group were reported as having SAEs categorized as cardiac disorders.

The largest imbalance within this category occurred in SAEs with a preferred term of acute myocardial infarction. Fourteen subjects in the Heplisav-B group and one subject in the Engerix-B group were reported as having an event with a preferred term of acute myocardial infarction.

In order to identify all events of myocardial infarction,

one needs to search for events that have slightly different preferred terms but actually represent events of myocardial infarction. The Standardized MedDRA Query, or SMQ, is a validated, predetermined set of MedDRA terms used to facilitate retrieval of MedDRA coded data as a first step in investigating safety issues.

The SMQ narrow for myocardial infarction was used to identify other possible myocardial infarctions reported in Study 23. Four preferred terms in the standard query, in addition to acute myocardial infarction, were identified in Study 23. They are listed on the left.

As you can see, acute myocardial infarction is the only preferred term that shows an imbalance between treatment groups, but when all of these terms are considered together, there continues to be an imbalance between the treatment groups with 19 subjects in the Heplisav-B group and 3 subjects in the Engerix-B group reporting at least one SAE for myocardial infarction.

Of the 19 subjects in the Heplisav-B group who reported a myocardial infarction identified by the SMQ, 13 were men and 6 were women. The mean age was 59.2. The median days from last active vaccination was 96 with a range of 3 to 329. Subjects had an average of 2.9 baseline risk factors, and 31.6% had a history of ischemic heart disease.

Of the three subjects in the Engerix-B group who reported

myocardial infarction identified by the SMQ, all were men. The mean age was 57. The median days from last active vaccination was 115 with a range of 13 to 203. Subjects had an average of three baseline risk factors, and all three had a history of ischemic heart disease at baseline.

In order to further evaluate the imbalance in myocardial infarctions that was observed in Study 23, the Applicant performed a major adverse cardiovascular events analysis, or MACE analysis.

The MACE composite endpoint was defined as subjects with events of cardiac disease, nonfatal myocardial infarction, and nonfatal stroke. Preferred terms were selected to identify potential MACE outcomes, and they were chosen in a blinded manner by Dynavax's consulting cardiologists. Serious adverse events with selected preferred terms were reviewed by consulting cardiologists external to Dynavax, and two consultants performed independent and blinded post hoc adjudication of all potential MACE events, and a third consultant was used in cases where there was a need for a tiebreaker. Consultants categorized events as a MACE event, not a MACE event, or insufficient information to make a determination.

Based on the adjudications by Dynavax consultants, there were 14 events of myocardial infarction in the Heplisav-B group and 1 event in the Engerix-B group in Study 23.

So this is a Kaplan-Meier curve that you've seen earlier today depicting the time from first vaccination to the time of event for adjudicated events of myocardial infarction.

The Heplisav-B group is shown in green, and the Engerix-B group is shown in black. As this only shows events adjudicated as myocardial infarction, some events identified by the preferred term query are not included in this figure. As you can see, the two groups diverge at approximately 3 months following the first dose, which would be 2 months following the second dose, and the difference persists through the remainder of the follow-up period.

There were 32 deaths reported in Study 23: 0.45% of Heplisav-B recipients and 0.25% of Engerix-B recipients died during the study. If you exclude deaths due to injury or illicit drug overdose, 0.29% of Heplisav-B recipients and 0.14% of Engerix-B recipients died during the study. No deaths were assessed as related by investigators.

Based on the selected preferred terms, 11 deaths in the Heplisav-B group and 3 deaths in the Engerix-B group were selected by Dynavax consultants for blinded adjudication. Three deaths in the Heplisav-B group and one death in the Engerix-B group were adjudicated as cardiovascular deaths. One death in the Heplisav-B group and two deaths in the Engerix-B group were adjudicated as not a cardiovascular death.

There were seven subjects in the Heplisav-B group and no

subjects in the Engerix-B group that had insufficient information surrounding their death for the adjudicators to determine whether there was a cardiovascular cause. And in general, these were subjects that were found dead more than 24 hours from the time they were last seen alive with no other direct information to indicate a specific cause of death.

To summarize the cardiac SAE findings in Study 23, there was an imbalance in SAEs categorized as cardiac disorders with more Heplisav-B subjects reporting such events compared to Engerix-B subjects. The imbalance was most notable with the preferred term of acute myocardial infarction. The imbalance persisted when other terms for acute myocardial infarction, as identified through a standardized list of terms, were included.

There is also an imbalance when only serious adverse events adjudicated as myocardial infarction by Dynavax are considered. All subjects with myocardial infarctions had one or more risk factors for cardiovascular disease. A difference between the treatment groups in events of adjudicated myocardial infarction is observed at 3 months following the first vaccine dose and persists throughout the study. And baseline risk factors for cardiovascular disease were balanced between the treatment groups.

A numerical imbalance in deaths not due to injury or illicit drug overdose is observed. This is not explained by deaths categorized as cardiac disorders. However, a greater

number of deaths in the Heplisav-B group were adjudicated as not enough information to determine whether the cause of death was cardiovascular.

Now I'm moving on to discuss adverse events of special interest. This slide is to show that the monitoring and evaluation of these events and the definitions of the terms describing them evolved during the course of development of Heplisav-B.

In Study 23, AESIs were defined by a pre-specified list of conditions that CBER considers potentially immune-mediated. The term AIAE, or autoimmune adverse event, was any MAE that was not on the AESI list but was evaluated by the SEAC as autoimmune.

In Study 16, the term "AESI" was not defined, but autoimmune adverse events were prospectively collected, and investigators were provided with a list of potentially immune-mediated conditions, which was essentially the AESI list.

In Study 10, immune-mediated conditions were not prospectively defined or collected.

So for the sake of integrating information across trials for this presentation, I'll define an AESI as any adverse event that's potentially immune-mediated, whether identified prospectively or retrospectively. AESIs may or may not be on the AESI list. And when I say potential AESI, I'm referring to an adverse event reported in Study 16 or 23, the studies that

prospectively monitored for AESIs, and the AE was suspected by the investigator to be an adverse event of special interest and was referred to a specialist and/or to the SEAC as required by the protocol.

In Study 23, subjects were monitored for AESIs through Week 56 following the first vaccination. Subjects with potential AESIs were referred to a specialist and to the safety evaluation and adjudication committee, or SEAC, for review and adjudication.

The SEAC was composed of one infectious disease and two autoimmune experts external to Dynavax. The SEAC was tasked with first answering the question, "Is the event an autoimmune disorder?" However, not all AESIs were considered autoimmune by the SEAC. For example, cranial nerve palsies are on the AESI list, but they were not considered autoimmune events by the SEAC.

Next, if the SEAC determined the event was autoimmune, they answered the question, "Is the event a new-onset autoimmune disorder?" And lastly, if it was autoimmune, "Is the event related to study vaccine?"

In Study 23, potential AESIs were reported in 0.7% of subjects in the Heplisav-B group and 0.8% of subjects in the Engerix-B group. These events were referred to the specialists and to the SEAC for adjudication.

Point three percent of subjects in the Heplisav-B group

reported events that the SEAC adjudicated as autoimmune and 0.4% of subjects in the Engerix-B group reported events that they adjudicated as autoimmune. And of these events, four subjects in the Heplisav-B group and zero subjects in the Engerix-B group reported events that the SEAC adjudicated as new-onset autoimmune events. And the SEAC did not adjudicate any events as related.

The four events that were adjudicated as new-onset autoimmune events were alopecia areata, ulcerative colitis, polymyalgia rheumatica, and hypothyroidism, which was diagnosed as autoimmune thyroiditis. The event of hypothyroidism was evaluated by the SEAC to be due to papillary thyroid cancer that was later diagnosed. The event of ulcerative colitis was assessed as serious. While no events were assessed as related by the SEAC, two events were assessed by investigators as possibly related: alopecia areata and polymyalgia rheumatica.

This table shows events that are considered to be AESIs by the FDA and were adjudicated by the SEAC as not autoimmune. There were five reports of Bell's palsy in five subjects in the Heplisav-B group. The event onset for Bell's palsy ranged from zero days after the second dose, which for this subject was 56 days following the first dose, to 256 days following the last active dose.

One subject who reported Bell's palsy had a previously reported diplopia diagnosed as a third cranial nerve palsy

while on study. Another subject was diagnosed with a sixth cranial nerve palsy. Both the third cranial nerve palsy and the sixth cranial nerve palsy in these two subjects were assessed by treating physicians and the SEAC as due to diabetes, though the investigator assessed the sixth cranial nerve palsy as possibly related.

One subject was diagnosed with Takayasu arteritis due to an incidental finding on a CT scan. The FDA obtained two external consultations regarding this case. The consultants both agreed that this event was correctly diagnosed as Takayasu arteritis but that the event was preexisting prior to study enrollment and there was no evidence of active disease following vaccination.

One event of granulomatous dermatitis was adjudicated as not an autoimmune event by the SEAC but is considered a new-onset AESI by FDA. The diagnosis was made based on a forearm biopsy, and the dermatopathologist recommended an evaluation for sarcoidosis that the subject declined. So it's being included here because it is an immune-mediated disorder and can be a marker for systemic disease and because sarcoidosis was not ruled out.

There were no events reported in the Engerix-B group that the SEAC determined were new-onset autoimmune disorders. There was one event in the Engerix-B group that the SEAC determined was not autoimmune but that it is a new-onset AESI, and this

was an event of Bell's palsy reported 27 days after the third dose and assessed by the investigator as possibly related.

So, in summary, there were three events in two -- or three events that are not included in the final count because, as per the narrative, a reasonable alternative plausible cause was identified.

New-onset AESIs without an alternative plausible cause were reported in nine subjects in the Heplisav-B group and one subject in the Engerix-B group. In the Heplisav-B group, this included five subjects with Bell's palsy and one subject each with alopecia areata, polymyalgia rheumatica, ulcerative colitis, and granulomatous dermatitis. And in the Engerix-B group, this included one subject with Bell's palsy.

So to summarize the safety findings in Study 23, overall, nonfatal SAEs and MAEs occurred at similar frequency between study groups.

An imbalance in SAEs of myocardial infarction was observed with more subjects in the Heplisav-B group reporting events. This is true for myocardial infarctions identified by standardized preferred term query and by those adjudicated by Dynavax blinded external consultants.

There was an imbalance in deaths not attributable to injury or illicit drug overdose, which is partially attributable to death in the Heplisav-B group for which enough information was not available to the adjudicators to make a

determination of whether or not it was a cardiovascular event.

And 0.16% of Heplisav-B recipients and 0.03% of Engerix-B recipients reported a new-onset AESI without alternative plausible cause.

Now I'm going to present an analysis of safety integrating information from Study 23 with other studies of Heplisav-B.

This table shows the varying length of follow-up of four different categories of adverse events in the three pivotal trials, Studies 10, 16, and 23, and the supportive studies.

Unsolicited adverse events were monitored for 28 weeks in both Studies 10 and 16 but were not collected in Study 23, and medically attended adverse events were collected through 56 weeks in Study 23 but were not collected in other pivotal trials.

SAEs were collected in all three pivotal studies but were monitored for 28 weeks in Study 10, 52 weeks in Study 16, and 56 weeks in Study 23.

AESIs were only collected in the pivotal trials 16 and 23, and due to the differences in safety monitoring in the three pivotal trials, the integrated analysis of safety focused on serious adverse events which were collected in the three pivotal trials and also on AESIs. AESIs were considered separately for studies that collected them prospectively versus studies that collected them retrospectively or evaluated them retrospectively.

The integrated summary of safety included three different safety populations for evaluation of SAEs. The primary safety populations, or PSPs, included a 6-month PSP and a 1-year PSP. The 6-month PSP included Studies 10, 16, and 23 and evaluated SAEs reported within the first 6 months following dose 1. The 1-year PSP included Studies 16 and 23 and evaluated SAEs that were reported for 1 year following dose 1. Study 10 was excluded from this analysis as SAEs were only collected for 6 months.

And the modified total safety population, or mTSP, included Pivotal Studies 10, 16, and 23 and Supportive Studies 14 and 22 and evaluated SAEs reported within the first 6 months following dose 1.

And I'll remind you that Study 14 and 22 were the supportive studies that used the final formulation dose and schedule of Heplisav-B proposed for licensure.

This table shows the number of subjects in the safety populations. So the 1-year PSP included Studies 16 and 23 and had 7,555 Heplisav-B recipients and 3,262 Engerix-B recipients. The randomization ratio for this study population is 2.3 Heplisav-B to Engerix-B.

The 6-month PSP also included Study 10 and had 9,365 Heplisav-B recipients and 3,867 Engerix-B recipients. The randomization ratio for this safety population is about 2.4 Heplisav-B to 1 Engerix-B. And the mTSP also included the

supportive studies and had 9,597 Heplisav-B recipients and because these studies were uncontrolled, there was also 3,867 Engerix-B recipients in the mTSP. So this presentation will focus on the primary safety populations.

Baseline characteristics of subjects receiving Heplisav-B and Engerix-B in the integrated analysis do not suggest selection bias based on age, sex, race, or Hispanic ethnicity.

In the 6-month PSP, the mean age of Heplisav-B recipients was 49.1 and Engerix-B recipients was 49.2. In the 1-year PSP, the mean age of Heplisav-B recipients was 51.3 and Engerix-B recipients was 50.9. Men and women enrolled at roughly equal rates in both primary safety populations, and a majority of subjects in both primary safety populations were white and non-Hispanic.

Baseline characteristics and conditions suggestive of increased cardiovascular risk also do not suggest selection bias. This table shows selected risk factors by study. Within each of the three pivotal trials, baseline risk factors between treatment groups were similar overall. However, the prevalence of these risk factors was greater in Study 23 than in the other two pivotal trials, and particularly when Study 23 is compared to Study 10.

There are some limitations to the pooling of studies, particularly to assess cardiovascular events. There were differences in the study populations of the three pivotal

trials with subjects in Study 23 having higher cardiovascular risk. There were also differences in randomization ratios. Study 23 was a 2:1 randomization, Study 16 was 4:1, and Study 10 was 3:1. Therefore, pooling of the pivotal trials disproportionately adds more low-risk subjects to the Heplisav-B group.

Now I'll present the results of the integrated analysis of safety.

Overall, serious adverse events were reported at similar rates between treatment groups in both the 6-month and the 1-year primary safety population. There were 34 deaths reported in the Heplisav-B clinical development program. All were discussed previously in this presentation: 32 reported in Study 23 and 2 reported in Study 16.

In the 6-month primary safety population, there were nine deaths in the Heplisav-B group and three deaths in the Engerix-B group that were not attributable to illicit drug overdose or injury. Based on the randomization ratio and the number of deaths in the Engerix-B group, you'd expect seven deaths in the Heplisav-B group.

In the 1-year PSP, there were 17 deaths in the Heplisav-B group and 5 deaths in the Engerix-B group that were not attributable to illicit drug overdose or injury. Based on the randomization ratio and the number of deaths in the Engerix-B group, you'd expect 12 deaths in the Heplisav-B group.

Because of the safety findings in Study 23, myocardial infarction and other cardiac SAEs were examined closely in the integrated analysis of safety. This table shows the serious adverse events of myocardial infarction as identified by the preferred terms in the Standardized MedDRA Query narrow for myocardial infarction, which I discussed previously.

The preferred terms are listed on the left with columns for each treatment group in Studies 23, 16, and 10 as you move from left to right. As we saw before, there were 19 subjects in the Heplisav-B group and 3 subjects in the Engerix-B group who reported myocardial infarction in Study 23. In Study 16, three subjects were identified with myocardial infarctions by preferred term search, two in the Heplisav-B group, and one in the Engerix-B group. The subject in the Engerix-B group had two adverse events with two preferred terms that represented the same event. And please keep in mind that this study had a 4:1 randomization ratio. And there were no events of myocardial infarction that were identified in Study 10.

This table shows the serious adverse events adjudicated as MACE events and identified in Studies 23 and 16 by the Applicant's MACE analysis. Event counts and percentage of subjects reporting events are identified in the first two columns for each study, and the third column for each study contains the relative risk of each MACE event and two confidence intervals.

The first confidence interval is the 95% Wald asymptotic confidence intervals supplied by Dynavax. The second confidence interval is the 95% Koopman score confidence interval. FDA's statisticians consider this a more appropriate confidence interval to evaluate events with low frequency such as the events of myocardial infarction in Heplisav-B trials. My colleague, Dr. John Scott, will give a presentation following this to further discuss the use of these confidence intervals.

When reviewing the number of events per group, please note that Study 23 had a 2:1 randomization ratio and Study 16 had a 4:1 randomization ratio.

So as we saw before for Study 23, starting in the second row, 3 subjects in the Heplisav-B group and 1 subject in the Engerix-B group had fatal SAEs that were adjudicated as cardiovascular deaths; 14 subjects in Heplisav-B and 1 subject in the Engerix-B group had a serious adverse event adjudicated as myocardial infarction; and 11 subjects in the Heplisav-B group and 4 subjects in the Engerix-B group had serious adverse events adjudicated as stroke.

For Study 16, there were few adjudicated MACE events. Two events were adjudicated as cardiovascular death, one in each study group, and two subjects in the Heplisav-B group and one subject in the Engerix-B group had a serious adverse event that was adjudicated as a myocardial infarction, and there were no

subjects that had an event that was adjudicated as stroke.

So there was a higher rate of MACE events in the Heplisav-B group compared to the Engerix-B group for Study 23. Dynavax's assessment is that the Bradford Hill criteria, including an assessment of temporality and plausibility, do not support causality, and there was a lower observed rate than expected, particularly in the Engerix-B group based on population-based data and risk prediction models that account for cardiovascular risk factors in these study populations.

However, please keep in mind that the findings were observed in a randomized controlled trial where the most valid comparison is to the Engerix-B group within the study and that the relative risk of myocardial infarction in Study 23 was 6.97.

So in order to assess -- in order to assist in the evaluation of the cardiovascular events observed, the FDA obtained three expert consultations, and I'll now summarize the conclusions of these three consultants.

Cardiologist Number 1 noted that there was an imbalance in myocardial infarction in Study 23 with more events in the Heplisav-B group. The imbalance of MI was not observed in previous studies, but Study 23 had a larger sample size and a higher percentage of cardiac risk factors compared to Study 16. Adjudicated stroke and cardiovascular deaths showed a similar direction as the MI imbalance, but there were few adjudicated

cardiovascular deaths and the relative risk was not robust. Kaplan-Meier curves for the MACE separate after 100 days post-first dose, suggesting no close temporal relationship.

Consultant Number 1 also stated that nonclinical and clinical studies failed to reveal a plausible mechanism of action for myocardial infarction. The risk of myocardial infarction could result from accelerated atherosclerosis, sustained increase in blood pressure, or some prothrombotic state, and none of these was in evidence.

The consultant noted that the Applicant's assessment that the event rate in the control is spuriously low is plausible, and it is also plausible that the between-group difference is spurious. The consultant concluded that there was a low likelihood that this was a reliable finding and a low absolute risk.

Cardiologist Number 2 noted the numerical imbalance in MI events between Heplisav-B and Engerix-B is moderately concerning. While the finding could be attributable to chance, the consultant could not confidently say that there was no increased risk of cardiovascular disease with Heplisav-B. Thus, the consultant believes that further evaluation is warranted.

The consultant noted that the Applicant's analyses are a reasonable first step, but their conclusions largely hinge on the low ratio of observed to expected events with Engerix-B in

the Phase 3 trials. That analysis has several limitations. The consultant stated it is difficult to place more weight on a comparison with externally derived event rates, such as the observed versus expected analysis, than on internal comparison between study arms.

Cardiologist Number 3 noted the Sponsor has observed an imbalance of ischemic cardiac events, mostly MI, associated with the use of its vaccine compared with an active control vaccine in a large randomized clinical trial. The trial was not prospectively designed to optimally identify suspected ischemic events, to have appropriately collected supporting materials on these events, nor to prospectively adjudicate suspected events. The trial did not enroll a group of patients at increased risk of cardiovascular events based on -- I'm sorry, the trial did enroll a group of patients at increased risk of cardiac events based on entry cardiac risk factor profiles. The consultant stated the Sponsor has performed a very reasonable series of analyses intended to explain or minimize this infrequent but troubling difference in cardiovascular risk.

The consultant goes on to note that the observation is consistent across several cardiac events, including unexplained death and myocardial infarction. The consultant stated in Study 23, the comparison of the MACE composite does not meet conventional statistical significance. And the consultant

concludes that the Sponsor cannot or does not fully eliminate the notion that this is a real observation worth further investigation, and the consultant agrees.

Further insights into possible cardiac risk associated with Heplisav-B require randomized comparisons and/or large postmarket observational studies with appropriate collection of suspected events, EKGs, biomarkers, and other records needed for event adjudication.

So moving on to unsolicited adverse events, these were not evaluated for the integrated analysis of safety. The prior review showed that the rates of unsolicited adverse events were reported in 55% of Heplisav-B recipients and 58% of Engerix-B recipients and that most were mild to moderate in intensity. But they did want to mention herpes zoster, that I previously mentioned, in the safety analysis for Study 23. In Study 10 and 16, unsolicited events of herpes zoster were reported in seven subjects in the Heplisav-B group and one subject in the Engerix-B group.

The randomization ratio for these two studies was approximately 3.5, so 0.2% of Heplisav-B recipients and 0.1% of Engerix-B recipients reported herpes zoster. And this is compared to the 0.7% Heplisav-B recipients and 0.3% Engerix-B recipients who reported the event in Study 23. And in Study 23, medically attended adverse events were monitored for twice as long as adverse events in Studies 10 and 16.

So moving on to AESIs, AESIs were collected prospectively in Pivotal Studies 16 and 23, and they both utilized SEAC adjudication. So I'll present an integrated analysis of these two studies here followed by analysis of studies that did not prospectively collect AESIs. So in Study 23 and 16, new-onset AESIs were identified in 15 subjects in the Heplisav-B group or 0.2%, and one subject in the Engerix-B or 0.3%.

Supportive Study 22 -- I'm sorry, I failed to mention that Supportive Study 22, which was an uncontrolled study, they used the final dose and formulation of Heplisav-B, also prospectively collected AESIs. And this study included 25 subjects where no AESIs were identified. And this study is included in the total denominators presented in the slide.

So this is to briefly remind you of the new-onset AESIs that were identified in Study 23, which I discussed earlier. And I would also like to point out the background -- estimated background incidences in the general population shown on the right-hand column. There were five events of Bell's palsy and one event each of alopecia areata, ulcerative colitis, polymyalgia rheumatica, and granulomatous dermatitis in the Heplisav-B group and one event of Bell's palsy in the Engerix-B group.

This slide shows the new-onset AESIs that were identified in Study 16. One event of Tolosa-Hunt syndrome was reported. This is a disease with an incidence of one in 1 million, and

I'll provide you with the details of that event shortly. Two events of hypothyroidism were adjudicated by the SEAC as new-onset autoimmune events. One event of erythema nodosum was adjudicated as not an autoimmune event but as related. One event of Bell's palsy was adjudicated by the SEAC as not an autoimmune event. And one event of vitiligo was reported in a subject with a prior diagnosis of psoriasis.

AESIs were evaluated retrospectively for studies that did not have a prospective identification and adjudication of events. I'm presenting them here separately.

So Dynavax searched the safety database of these trials for preferred terms from the list of AESIs that was used in the studies that prospectively collected AESIs. So I'd like to note that this evaluation includes studies that did not use the final formulation dose or schedule. In these studies, new-onset AESIs were identified in six subjects in the Heplisav-B group, or 0.2%, and in five subjects in the Engerix-B group, or 0.5%.

This table shows the AESIs that were identified in these studies. One subject in the Heplisav-B group in Study 10 was diagnosed with granulomatosis with polyangiitis, which is formerly Wegener's granulomatosis. One subject in the Engerix-B group in Study 10 with a past history of another autoimmune disorder was diagnosed with a p-ANCA positive vasculitis. And I'll provide you with the details of these two

cases in a moment. One subject was diagnosed with Guillain-Barre syndrome in 110 days after the last active dose of Heplisav-B and 5 days after an influenza vaccine.

Other events in the Heplisav-B groups included Grave's disease, lichen planus, Bell's palsy, and uveitis. Other events in the Engerix-B group included Bell's palsy, Grave's disease, Raynaud's phenomena, and rheumatoid arthritis.

Now I'm going to present the details of the three AESIs that I mentioned. The first two cases were presented at the November 2012 VRBPAC.

One subject, who received Heplisav-B in Study 10, was diagnosed with granulomatosis with polyangiitis, or formerly Wegener's granulomatosis. This subject was a 55-year-old woman with no significant medical history who reported widespread urticaria 18 days after dose 1. She received dose 2 as scheduled; she reported a recurrent sinusitis that began approximately a month and a half after dose 2. Six months after dose 2, she was admitted for sinusitis and found to have pulmonary infiltrates, pleural and pericardial effusions, and glomerulonephritis. Testing was positive for proteinase 3 c-ANCA, at which time the diagnosis was made. A retrospective analysis of banked serum showed negative testing for ANCA at baseline, weakly positive proteinase 3 ANCA 4 weeks after dose 1 and 4 weeks after dose 2, and increasing in positivity after that. The investigator's assessment was that the event

was possibly related to study treatment.

The second case involves a 44-year-old woman with a medical history that included a 10-year history of mixed connective tissue disease, osteoarthritis, food allergy, and headache. She was enrolled in Study 10 and received Engerix-B. The mixed connective tissue disease was undisclosed at study enrollment, but it was later learned that the subject had been previously treated for over 2 years.

Approximately 3 months following dose 2, she reported fever and malaise, was treated for pneumonia, but also reported pleuritic pain that did not resolve. Approximately 4 months after dose 2, she developed a pulmonary hemorrhage and was admitted and intubated. A blood test revealed positive myeloperoxidase p-ANCA, leading to a diagnosis of p-ANCA positive vasculitis. Retrospective testing of banked serum samples revealed that ANCA was negative until the time of diagnosis. Retrospective testing also revealed a baseline ANA of greater than 1 to 5,120. The investigator's assessment of the event was that it was not related to study treatment.

A 68-year-old man with hypertension, gastroesophageal reflux, ruptured cervical disc, back surgery, and gunshot wound to the left chest was enrolled in Study 16 and received Heplisav-B. Approximately 5 months after dose 2, he reported decreased visual acuity; approximately 7 months after dose 2, he reported left frontal headaches; and approximately 9 months

after dose 2, he was hospitalized with double vision, headache, left facial numbness, and was found to have a left-sided ptosis, photophobia, and deficits in the first division of cranial nerve V and left-sided cranial nerve VI palsy.

His symptoms responded to high-dose steroids. He had multiple imaging studies that did not show evidence of cavernous sinus inflammation. He was diagnosed with Tolosa-Hunt syndrome, which was captured as cavernous sinus syndrome in the datasets. Tolosa-Hunt syndrome is a rare syndrome of painful ophthalmoplegia caused by idiopathic granulomatous inflammation of the cavernous sinus. There was no tissue diagnosis of granuloma in this case, although this is not necessary to make a diagnosis. The investigator's assessment was that the event was not related to study treatment.

Following the November 2012 VRBPAC, FDA obtained four specialist consultations given the question regarding the diagnosis of Tolosa-Hunt syndrome and the possibility of two subjects in the Heplisav-B group reporting rare presumably granulomatous diseases. All four consultants agreed that the case -- assessed the case as Tolosa-Hunt syndrome, each of them noting the response to steroids and reasonable exclusion of alternate etiologies.

Of the three consultants that commented, two did not believe there was evidence of overlap between Tolosa-Hunt syndrome and granulomatosis with polyangiitis. One consultant

noted that there can be overlap but that in this case of Tolosa-Hunt syndrome reported in Study 16, they did not display features that the consultant would expect if it were granulomatosis with polyangiitis. Of the three consultants that commented, none endorsed a causal association between the vaccine and the adverse event.

So this slide is to remind the current VRBPAC of what was discussed at the November 2012 meeting and to update the Committee with information from 23. So there was no clear clinically significant trends that were noted in the results of laboratory investigations post-vaccination, and these laboratory evaluations included hematology, chemistries, ANA, anti-double stranded DNA, ANCAs, complement components C3 and C4, erythrocyte sedimentation rate, and urinalyses evaluated in different studies.

So now I'm going to summarize the integrated safety data submitted in support of licensure.

Prior review of the data submitted for the BLA did not reveal any clinically significant differences between Heplisav-B and Engerix-B recipients in local and systemic solicited adverse events and in laboratory investigations.

In the currently available safety data submitted, overall nonfatal serious adverse events occurred with similar frequency between treatment groups. There was a numerical imbalance in deaths and in deaths not attributable to illicit drug overdose

or injury in the 6-month and 1-year primary safety populations.

There was an imbalance between treatment groups in serious adverse events of myocardial infarction observed in Study 23, with 19 subjects in the Heplisav-B group and 3 subjects in the Engerix-B group reporting SAEs with the preferred term as identified by the standardized query for myocardial infarction.

Because of this imbalance, a major adverse cardiovascular events analysis, which included blinded adjudication of events of cardiovascular death, MI, and stroke in the three pivotal trials, was conducted. The MACE analysis showed that in Study 23 there were 14 subjects in the Heplisav-B group and 1 subject in the Engerix-B group who had an SAE adjudicated as MI. And differences between treatment groups in events of adjudicated cardiovascular death, although few, and adjudicated stroke trended in the same direction.

An imbalance in myocardial infarction in the composite three-point MACE outcome was not observed in other trials. However, Studies 16 and 10 enrolled populations with lower prevalences of known risk factors for cardiovascular disease. The difference in risk between treatment groups was noted approximately 3 months after first vaccination, which is 2 months after second vaccination, and persisted through the study follow-up period. Subjects who reported myocardial infarctions all had risk factors for cardiovascular disease. Reported risk factors were similar between treatment groups at

baseline within each study, and Dynavax attributes the finding that there was a lower than expected rate of myocardial infarction in the Engerix-B group to chance.

With respect to AESIs, they were evaluated prospectively in Studies 16 and 23 and referred to the SEAC for adjudication. In these two studies, 15 new-onset AESIs were identified in the Heplisav-B group and 1 new-onset AESI in the Engerix-B group. AESIs were identified retrospectively across most of the other trials and were therefore not adjudicated. So by selected MedDRA preferred term, the incidence of unadjudicated new-onset AESIs in these studies was greater in Engerix-B group.

Rare and serious AESIs were reported among Heplisav-B recipients, specifically granulomatosis with polyangiitis, Tolosa-Hunt syndrome, and Guillain-Barre syndrome. And the rare and serious AESI of p-ANCA positive vasculitis was reported in a subject in the Engerix-B group who had a preexisting diagnosis of mixed connective tissue disease.

Limitations to the integrated analysis of safety and assessment of the observed events include issues with pooling, a lack of prospective monitoring of specific events that were identified as potential risks, and limited ability to assess rare events. Pooling of trials combines study populations with different characteristics and risk. And this was demonstrated by the different prevalences of cardiovascular risk factors between the three pivotal trials.

Similarly, pooling of studies to assess AESIs is difficult given the evolution in defining, collecting, and evaluating these events.

Cardiovascular events were not collected prospectively in any of the studies. AESIs were not collected prospectively in several studies. This potentially led to under-ascertainment of events. For example, for cardiovascular events, EKGs were not collected, and thus silent myocardial infarctions were unlikely to be captured.

And, finally, for rare events such as autoimmune diseases, large sample sizes are necessary for statistically robust assessment of risk.

So Dynavax has submitted a comprehensive pharmacovigilance plan which includes routine pharmacovigilance of postmarketing safety study and a pregnancy registry. I'm going to focus on the postmarketing safety study.

The proposed study aims to assess the risk of anaphylaxis and important potential risks, that is cardiac events, immune-mediated diseases, and herpes zoster following Heplisav-B administration.

The proposed retrospective cohort study using electronic healthcare databases will be conducted at Kaiser Permanente Northern and Southern California to which Dynavax would provide Heplisav-B free of cost. The study will compare the incidence rates of cardiac events, pre-specified immune-mediated

diseases, and herpes zoster in 20,000 Heplisav-B recipients compared with those in 20,000 recipients of other monovalent hepatitis B vaccines.

The cohorts will be followed for up to 13 months following the first vaccination. Dynavax-based preliminary data provided by Kaiser has suggested that it may be possible to complete recruitment of the cohorts within 1 year; thus, the final results may be available 3 to 3½ years after study initiation.

As per the Applicant, the proposed study would provide 99% power to exclude a hazard ratio of 2 or higher for MACE events after 2 years following study initiation, assuming a background incidence rate of 6 per 1,000 person-years. The study will provide 87% power to exclude a hazard ratio of 2 or higher for acute myocardial infarction. It would provide 87% power to exclude a relative risk of 2.5 or higher for the 36 pre-specified immune-mediated diseases assessed jointly, assuming a background incidence rate of 1 per 1,000 person-years.

The analysis will also be performed for each event of interest separately. For these analyses, the power would be limited since, for example, the background incidence rate for granulomatosis with polyangiitis is approximately 0.8 to 1 per 100,000 person-years and the background incidence for Tolosa-Hunt syndrome has been assessed as approximately 1 to 2 per 1 million person-years.

And, finally, the study would provide 99% power to exclude

a hazard ratio of 2 or higher for herpes zoster after 2 years after the study starts assuming a background incidence rate of 4 per 1,000 person-years.

And now I'll just remind you of the questions to the Committee.

Do the available data support the safety of Heplisav-B when administered to adults 18 years and older? Please vote yes or no.

If yes, please comment on the proposed pharmacovigilance plan. If no, do the presented data support usage in a more specific subpopulation? Please vote yes or no.

What additional studies (pre- and post-licensure) are needed to further evaluate the safety of Heplisav-B in the general adult population and/or in specific subpopulations?

Thank you.

DR. EDWARDS: Thank you.

Are there questions for Dr. Everett?

Yes, Ofer.

DR. LEVY: Thanks for that. So in the proposed post-licensure study at Kaiser, from the Sponsor's proposed -- if that's what I understand you're presenting, that would be, in their view, in the context of licensure so that the adjuvanted vaccine would be broadly released under that scenario to the entire population with this kind of study nested in that that would then enroll 40,000; is that the big picture?

DR. EVERETT: I'm going to ask my colleague, Dr. Perez-Vilar, to help me address that question.

DR. PEREZ-VILAR: Silvia Perez-Vilar.

What the manufacturer has proposed is to provide a heavily -- to Kaiser Permanente Northern California, Southern California after consultation with them, and they believe that they will be able to include 40,000 patients within 1 year.

DR. LEVY: No, but my question is that proposal -- I'm just trying to understand the proposal on the part of the Sponsor, so that proposal would be a post-licensure? So if I understand that correctly, that would mean that the vaccine Heplisav would be licensed, available to the entire United States.

DR. PEREZ-VILAR: Yes.

DR. LEVY: And, in addition, there would be this piece at Kaiser where one would look more carefully at the concerns for these endpoints. Is that what is being proposed?

DR. PEREZ-VILAR: Yes, this is if the vaccine is approved.

DR. LEVY: And would this proposal include monitoring the results at Kaiser as they came in so that if there was a big imbalance it could be stopped earlier?

DR. PEREZ-VILAR: What the manufacturer has proposed is enroll patients within 1 year so they follow up, and since the first patient will be included, they will -- the study 25 months afterwards. But through several communications, they

will provide interim result at 12 months, 18 months, 25 months, and final results could be at a level around 3.3, 3.5 years if the recruitment is possible to be accomplished within 1 year.

DR. LEVY: Again, just sorry for the follow-up, I'm just trying to understand the proposal. So that information at 12 months, for example, would be provided to FDA?

DR. PEREZ-VILAR: Yes.

DR. LEVY: And then FDA would review that presumably if there were concerns about disparities in these directions. FDA would then have the power to do something about it if they needed to?

DR. PEREZ-VILAR: It depends if first, if the vaccine is approved and this is PMR and so -- and we can establish the study groups, if this is your question.

DR. EDWARDS: Dr. Monto.

DR. MONTO: Since we're getting clarification, could you show the next PowerPoint for 3? Do we have any proposal for what the specific population would be?

DR. GRUBER: So this is Marion Gruber.

So what we were -- what we're thinking to do is let's say you vote yes, that the presented data support usage in the more specific subpopulation, the Chair of VRBPAC would then query you to opine on what subpopulations are -- or what subpopulations the data would support. So, in other words, this would not be a further voting question. It's just let's

say you say yes, there could be use of the vaccine in a subpopulation, then the Committee would discuss what specific populations you'd have in mind.

DR. MONTO: So this is still an open question?

DR. GRUBER: That would be still an open question. That would not be a vote.

DR. EDWARDS: Yes, Karen.

DR. KOTLOFF: I'm just still kind of a little bit stuck on how the vaccines will be allocated in this retrospective study and how we will be able to either avoid doing the evaluation in a low-risk group that wouldn't give us the answer or having some type of bias in the populations who get either vaccine that would make the data very difficult to interpret.

DR. EDWARDS: FDA is going to comment.

DR. PEREZ-VILAR: We have asked the manufacturer, and they have asked Kaiser Permanente, and this is one of the concerns basically because we don't know how the vaccines are going to be allocated. So as acknowledged by Dynavax, they believe that people with diabetes or -- risk factor for cardiovascular in -- for cardiovascular events maybe would be more likely to receive Heplisav than the comparator vaccine. So we don't know if both cohorts will be comparable. It could be, in fact, completely comparable.

DR. EDWARDS: Dr. Packer.

DR. PACKER: This is the same question. First of all,

it's not a retrospective cohort study; it's a prospective cohort study, I think.

(Off microphone comment.)

DR. PACKER: Yeah, the Kaiser, right. The slide before said retrospective. But here's the question, and I imagine that for purposes of full disclosure that the imbalance in myocardial infarction would appear somewhere in the labeling. If that were true, if that were true, then one might think that physicians would selectively use this particular new vaccine in a lower-risk population and then forcing the Sponsor to use some covariate analysis in order to see if the two populations could be made to be comparable. How do you solve a problem like that?

DR. PEREZ-VILAR: The outcomes could be collected retrospectively. The accrual will last 1 year, but after 1 year, they will identify the outcomes retrospectively, okay.

DR. PACKER: Yeah.

DR. PEREZ-VILAR: And the second question, please, can you --

DR. PACKER: If the vaccine is approved and if the label describes the imbalance in myocardial infarction, if there would be a likelihood that physicians might selectively administer this vaccine to patients at lower cardiovascular risk, how do you then make the two populations comparable?

DR. PEREZ-VILAR: This is one concern that I share with

you. The manufacturer has proposed to use stratification -- to try to make -- to adjust for these differences, these potential differences in risk.

DR. EDWARDS: Dr. Monto.

DR. MONTO: The simple solution would be age -- limiting it to certain age groups because if there is very little use in the population at risk, there's no way in analysis that you can get to the issue.

DR. EDWARDS: Dr. Janssen, would you like to comment?

DR. JANSSEN: Yeah, distribution of the vaccine in Kaiser and how it would be done has not been decided. They do appear to have the ability to essentially do what's -- they can distribute it to some facilities and not other facilities. So it's essentially there is a potential for a quasi-cluster randomization.

DR. EDWARDS: Dr. Griffin.

DR. GRIFFIN: Yeah, I mean, I think that's what I was -- can there be a pragmatic clinical trial postmarketing, or can that be a requirement, to have more of a pragmatic clinical trial?

DR. PACKER: It's not a pragmatic clinical trial; it's a cluster randomization. So Kaiser would essentially randomize their medical institutions. Some would get the vaccine, some would not get the vaccine. It's not a pragmatic trial because pragmatic trials are -- well, they're defined differently than

that. It's a practical trial but not a pragmatic one.

DR. EDWARDS: Karen, and then we'll hear the safety -- or the statistical analysis.

DR. KOTLOFF: I just wanted to also raise a concern that if one of the major public health benefits of this vaccine is to have the higher-risk people be more likely to be completely vaccinated but there is a caution in vaccinating those people, I'm just wondering how that will be reconciled.

DR. EDWARDS: Good point.

Other comments?

Yes, Dr. Janssen.

DR. JANSSEN: So the numbers were small, but I do want to point out that acute myocardial infarctions in diabetics in HBV-23 were two in the Heplisav group, one in the Engerix group in a 2:1 randomization.

DR. PACKER: You think that that's a reliable estimate?

DR. JANSSEN: No, I don't.

DR. PACKER: Okay, thank you.

(Off microphone comment.)

DR. PACKER: I get it, yeah.

DR. EDWARDS: All right, let's have the final presentation from the FDA, the statistical analysis. This will be presented by Dr. John Scott, the Acting Director of the Division of Biostatistics in the Office of Biostatistics and Epidemiology at CBER.

DR. SCOTT: Thanks. Hello, my name is John Scott. I'm the Acting Director of the Division of Biostatistics at CBER. I'm going to be presenting FDA's statistical evaluation of the risk of acute myocardial infarction associated with Heplisav-B today.

I'm going to start with a discussion of the confidence interval approaches for the relative risk of AMI for Heplisav-B versus Engerix-B, and then I'm going to be presenting some alternative simple Bayesian analyses that we performed of the relative risk.

So, in general, there are several different possible methods for calculating confidence intervals for relative risks. The Applicant's calculations have used what's called the Wald method, which is popular in part because it's computationally very simple, but it's well established in the statistical literature that it performs poorly and is conservative when the event counts are very low as they are in this case.

In this case, for a confidence interval, conservative means that the interval is too wide. So we calculated Koopman score intervals as an alternative based both on the literature and on some simulations we performed. In this particular setting, these intervals have much closer to the coverage that they're supposed to have, that is a 95% interval really is a 95% interval. The Wald interval is a 95% interval, and it

might be closer to a 98% interval here.

So these are the major cardiovascular events in study HBV-23. In particular, for AMI we see the 14 events for Heplisav-B and the one event for Engerix-B with a relative risk of 7, and the Applicant's calculated confidence interval goes from 0.9 to 52.97. FDA's recalculated confidence interval goes from 1.17 to 41.44.

There are some things that are important to keep in mind with interpreting confidence intervals in this setting. If we were talking about a pre-specified safety outcome, we would generally be talking about the upper confidence limits, and that would be interpreted as the level of risk that was ruled out by the data. The lower confidence limits in general are less relevant in that setting, largely because the tests of the null hypothesis of no difference are underpowered for low event rates. But this is not a pre-specified safety outcome; this is an unexpected safety finding, and confidence intervals are just generally difficult to interpret in this setting. That's largely because of the implicit multiple testing problem; there were many possible safety outcomes that could have resulted in a signal, and due to regression to the mean, which is closely related, we are looking at one of the largest of the signals.

As an alternative to the confidence interval analyses, we performed a simple Bayesian analysis of the relative risk of AMI for Heplisav-B versus Engerix-B, and the advantages of this

approach is that it lets us explore different levels of borrowing information from previous studies, and it also allows direct probability interpretations of where the true value of the relative risk is likely to be.

Because Bayesian analyses may be less familiar to some of you, this is just a one-slide very, very high-level overview of how this works. So Bayesian approaches are often used to synthesize existing data with new data in order to form updated probability distributions of the likely values of quantities of interest. The existing data in this setting are summarized in what's called a prior probability distribution, and the results are expressed as a posterior probability distribution. That's a probability distribution for the parameter that we care about after taking into account both the data and the prior distribution. In that sense, posterior distributions are always a kind of compromise between the prior belief or the prior distribution and the new data.

So in the Heplisav-B case, we used studies HBV-10 and HBV-16 to form prior distributions of the risk of AMI for Heplisav-B and Engerix-B, and we updated those distributions using the data from study HBV-23 to form posterior distributions for the relative risk of AMI.

We looked at a variety of scenarios of borrowing, but we're presenting two scenarios today: first, a full borrowing scenario, which is essentially roughly equivalent to pooling

all three studies to get at the AMI relative risk, and then a no-borrowing scenario where we're only using data from study HBV-23 with what are called non-informative prior distributions. Any other potential borrowing scenario would fall somewhere in between these two cases.

So these are the data that we're talking about. You've seen versions of this table several times today. When we're talking about a no-borrowing scenario, that's based only on the 14 to 1 events of AMI in study HBV-23, and the full borrowing scenario is based on that same 14 to 1 plus the 2 to 1 in study HBV-16 along with the total denominator from all three studies.

We've also included some of the cardiovascular risk factors on this slide to provide a context for thinking about the poolability of the data.

So these are the results from the full borrowing scenario. This is the posterior distribution of relative risk. What this shows is that based on all three studies together, the posterior probability that the relative risk is greater than 1 is 94.7%, the posterior probability that it's greater than 2 is 65.5%, the posterior probability that it's greater than 3 is 40.8%, and the posterior probability that the relative risk is greater than 5 is 17.3%. So that's the full borrowing scenario.

This is the no-borrowing scenario just based on the HBV-23 data. Now, the relative risk that the -- I'm sorry, the

probability that the relative risk is greater than 1 is 98.6%, the probability that it's greater than 2 is 85.5%, the probability that it's greater than 3 is 68.8%, and the probability that it's greater than 5 is 43.3%.

As with the confidence intervals, there are important caveats to interpreting these posterior probabilities, essentially the same caveats.

First of all, these results are based only on the cumulative incidence data of AMI from the three studies, just like the confidence interval analyses. So this doesn't take into account additional external factors such as many of the causal criteria that we've heard about from the medical experts today and also the possibility of regression to the mean.

What this does do is it provides a range of possible relative risk probabilities just within the scope of what the number of events from the three studies tells us in isolation from other considerations.

Thank you.

DR. EDWARDS: Thank you very much.

Are there questions? Comments?

Dr. Lee.

DR. LEE: Yes. Thank you for the interesting study. I wonder whether FDA or you have done the time-to-event analysis because the talk mostly today are frequency of events. The time-to-event analysis can take into account lost to follow-up,

censor, and so -- and also sometime can take into account the covariate to some stratified analysis.

DR. SCOTT: Yeah, that's a good question. We haven't looked at it in great detail. We have produced Kaplan-Meier plots that you've seen; also, the Applicant presented some Kaplan-Meier plots. We haven't done specific analyses of the hazard ratio that I have to present today, though.

DR. LEE: Yeah, the Kaplan-Meier plot, we can do some tests, and if without waiting the time, the ratio is inconclusive, but if you take into account the time, like a Fleming-Harrington test, then the hazard ratio would be maybe higher. So really time may be important.

DR. SCOTT: I think that's a very good point in terms of interpreting the data; however, we probably wouldn't have focused on a significance test again because of the multiple testing, regression to the mean issue.

DR. LEE: Thank you.

DR. EDWARDS: Dr. Sawyer.

DR. SAWYER: Yeah, could you just recap, for the non-statistically inclined here, to what extent you have mitigated against the multiple effects issue because that seems to be the most compelling issue for me is statistic.

DR. SCOTT: It's an easy answer. To no extent at all. This is purely looking at this relative risk in isolation from all other considerations. There's no straightforward way to

know how much to adjust for the multiplicity in a post hoc setting like this, so we essentially cannot do it.

DR. EDWARDS: Dr. Packer.

DR. PACKER: Just one question of curiosity. When you're calculating your priors, for the study with zero-zero events, is that assumed to provide no information or neutral information?

DR. SCOTT: That does provide information. It provides information of nonevents happening in both arms when we're borrowing from that study. In the full-borrowing scenario, the prior distribution that we use to interpret HBV-23 is based on the number of events and the denominators for Studies 16 and 10 combined. So it does go into the denominator.

DR. EDWARDS: Any other questions?

DR. KOTLOFF: I have one question.

DR. EDWARDS: Karen.

DR. KOTLOFF: Did you do any similar type of analysis looking at the autoimmune, the probability of the autoimmune events being real?

DR. SCOTT: We did not. There are -- no, that's an interesting question. We didn't.

DR. EDWARDS: Questions?

(No response.)

DR. EDWARDS: Okay, I would like to propose, then, that we break for lunch, that we regroup at 1:30, which is not the full

hour. We have at least 17 people that want to comment in the Open Public Comments, and their comments will be kept to between 1 to 2 minutes. At the end of 2 minutes, I will announce the next speaker, so I'm going to play by the rules, so we do need to move quickly.

We also have a number of individuals that will need to leave later in the afternoon, so we do have to be expeditious about our time. So let's break and regroup at 1:30.

(Whereupon, at 12:50 p.m., a lunch recess was taken.)

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

(1:30 p.m.)

DR. EDWARDS: Seated, and we'll begin the Open Public Hearing of the registered speakers.

Okay, Dynavax has asked us to give them a little bit of time to address some questions that we had asked, so they are going to expeditiously address those questions, and then after that is going to happen, then we will have a very prompt Open Public Hearing that will be very terse as well.

DR. JANSSEN: So it's one comment. There was discussion about --

DR. EDWARDS: Please.

DR. JANSSEN: -- how many people would be vaccinated in the first year, so if we're approved, we'll do the postmarketing study and then it would be available. This is a very tight commercial market that's very -- that access to it is tough, and in the first year we think probably we may vaccinate up to 75,000 people including the people at Kaiser. So I just wanted to let people know what we think the probable realistic numbers are for the first year.

DR. EDWARDS: Okay. And have you thought specifically about the distribution of those subjects or not at this time?

DR. JANSSEN: For Kaiser, no. We've been having those conversations, but the way we'd really like to do it is to have them distribute it to different facilities so that -- so they

work more as a control.

DR. EDWARDS: Okay, so we have to read this, right? Okay.

So the Open Public Hearing announcement: Welcome to the Open Public Hearing session. Please note that both FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee, the FDA believes it's important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships you have with the sponsor, its product, or if known, its direct competitors, for example, if the information includes sponsor's payment of your travel, lodging or other expenses. Otherwise -- likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have such relationships. If you choose not to address this at the beginning, it will not preclude you from speaking.

So I will name a series of people who have registered for the Open Public Hearing, and please come up and present, and make it no longer than 2 minutes. If it's longer than 2 minutes, I will interrupt you.

So the first speaker will be Robert Perrillo from Baylor University College of Medicine.

DR. PERRILLO: Thank you. My travel here today was subsidized by Dynavax, but I would've come under my own resources at any matter because I feel that this is an important issue.

We have a lot of patients that I see in my practice, which is dedicated at this point in my career exclusively to hepatitis B, who really fail to have adequate medical care on a regular basis. I know this is largely amongst the family and household members that live with index cases of hepatitis B that are born outside of the United States.

So I think a vaccine like this that can be successful in two doses is going to really improve on a miserable completion of vaccine rates that we have in the at-risk populations. I also think it will have other potential uses because it's immunogenic, in the future, because there are people that do need expedited SPR besides the military, people that would be undergoing chemotherapy and have had hepatitis B in the past, it might reactivate their infections otherwise.

So I think that the major point that I would make out of the increased immunogenicity is that it's simpler, it's going to lead to more complete vaccination rates, and also that it will also speed up the process substantially for people that need protective antibodies quickly.

DR. EDWARDS: Thank you very much.

The next speaker will be Judy Weisman.

DR. WEISMAN: My name is Judith Weisman. I am the medical director of a methadone maintenance clinic in Rockland, Maine, which is in Midcoast, and in this august body of academicians and researchers, I represent boots on the ground, or in the mud, depending on the season. I deal with drug addicts on a daily basis. This is, by definition, a high-risk population.

Interestingly, most of the transmission of the hepatitides among my patients is because of heterosexual sexual activity. When I ask about have they shared needles, they look horrified, "I would never do that," and you can buy needles over the counter in Maine. When I've asked them, well, how about would you be interested in a vaccine that requires two doses over a 1-month period rather than three doses over a 6-month period, they look at me as if I have three heads. "Well, doc, you know, I don't like coming in here. Of course, I'd do it in two doses rather than three."

And if there's increase in immunogenicity, to me this is close to being a no-brainer. My patients would be interested in this, I certainly would be interested in this, and yes, I have to -- Dynavax did pay for my travel, I forgot to mention. Other than that, no, I'm not being reimbursed. So that's the word from the -- in-the-trenches doc. Thanks.

DR. EDWARDS: Thank you so much.

The next speaker will be Megan Polanin.

DR. POLANIN: Thank you for the opportunity to speak

today. My name is Dr. Megan Polanin, and I'm a Senior Fellow at the National Center for Health Research. Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policy makers. We do not accept funding from industry, so I have no conflicts of interest today.

Like any public health strategy, a vaccine's benefits must outweigh the risks. One of the major benefits of Heplisav-B is that the shorter dosing schedule could improve vaccination rates. However, the clinical trials have raised serious concerns about safety for some patients.

We commend the FDA for closely analyzing the safety data and agree that the affect on adverse events is unclear. We support the FDA's diligence in working with the company to develop future studies needed to address these safety concerns.

We commend the company for including more black patients in HBV-16 and HBV-23 as this group has a relatively high incidence of acute hepatitis B infection. However, Asians living in the United States account for more than half of the 1 million Americans living with chronic hepatitis B. Chronic infection is responsible for most HBV-related morbidity and mortality. Clearly, Asians are not adequately represented in the company's pivotal trials. There's no way to know if the impact of the vaccine would be different for any Asian groups because too few Asians are included in the study.

In addition, the clinical trials took place in different countries with varying numbers of patients with diabetes, high BMI, or a history of smoking. These factors could also affect the risk-benefit ratio.

We feel for the company because it has previously tried and failed to obtain approval; however, the bottom line is we don't know how safe the vaccine is overall and specifically how safe it is for Asians who comprise the majority of patients living with chronic hepatitis B.

It is better for FDA to be cautious rather than approve a potentially dangerous vaccine, especially because other options are available. We strongly urge this Advisory Committee to prioritize patient safety and urge the FDA to maintain its scientific safety standards for approval and therefore recommend additional pre-licensure studies to further evaluate the safety of Heplisav-B in subpopulations who are disproportionately affected by both acute and chronic hepatitis B infection.

DR. EDWARDS: Thank you very much.

Dr. David Thomas.

DR. THOMAS: I have no conflicts of interest to disclose, and I'm going to read my comments in the interest of time.

As a physician caring for adults with infectious diseases and an epidemiologist aware of the public health impact of viral hepatitis, I strongly support HBV vaccine development.

Hepatitis B is a major public health problem that's preventable, and yet many adults remain at risk of infection. For example, in the most recent representative sample of the U.S. general population, vaccine-induced protection against hepatitis B was noted in just 29% of adults 20 to 50 years of age and just 9% of those more than 50.

HBV infections continue to occur among adults, and the incidence has actually risen in association with the national opioid outbreak. New infections also continue to occur among persons with diabetes, high-risk same-sex and heterosexual exposures, and among persons who inject drugs. And we are seeing a resurgence of relapsing infections brought on by the expanding use of immunosuppressive agents.

Unfortunately, the immunogenicity and completion rates of the current HBV vaccines are lower in many of the same populations who most need protection, including persons with diabetes, those on dialysis, and HIV-infected persons compared to healthy adults or children. For example, in most real-world settings, only 55 to 60% of persons complete their vaccine series, and even among those who do, 10 to 40% may fail to achieve protective immunity.

Therefore, from a clinical and epidemiologic perspective, we enthusiastically support development of more immunogenetic and simpler vaccine products for our adult patients.

DR. EDWARDS: Thank you very much.

The next speaker will be Ryan Clary.

MR. CLARY: Good afternoon. I have no financial relationship with Dynavax.

My name is Ryan Clary, and I'm the Executive Director of the National Viral Hepatitis Roundtable. We are a coalition of over 500 organizations around the country working to fight and ultimately end the hepatitis B and C epidemics in the United States. As you review this application, I ask that you consider the following points:

First and foremost, hepatitis B disproportionately affects Asian American and Pacific Islanders. Hepatitis B affects 1 in 12 AAPIs, and while Asian Americans and Pacific Islanders make up 5% of the U.S. population, they account for more than 50% of the hepatitis B cases in the country. These are unacceptable statistics that require a sense of urgency in providing new effective prevention tools in order to address a serious health inequity.

In March 2017, the National Academies of Sciences, Engineering, and Medicine released a national strategy for the elimination of hepatitis B and C, stating emphatically that the public health impact of hepatitis B and C could be eliminated by the year 2030 and outlining specific recommendations to lead the nation towards this goal.

One of the recommendations calls for expanded access to adult hepatitis B vaccination, noting that as of 2014, only a

quarter of adults over the age of 19 were fully immunized. The public health benefit of a two-dose over 1-month hepatitis B vaccine would move the United States forward in achieving elimination goals.

In May 2017, the CDC released disturbing statistics showing a 20% increase in acute hepatitis B infections in 2015. The increase is largely the result of injection drug use tied to the nation's opioid crisis. An effective vaccine with fewer doses taken over a shorter period of time could be provided to at-risk adults at syringe access programs, substance abuse treatment services, and other appropriate settings to protect them from a serious and sometimes fatal disease and to slow or stop new infections.

Finally, I would like to share a personal story that led me to this work. In March 2001 my partner was rushed to the emergency room with internal bleeding. Five days later he learned he had chronic hepatitis B and inoperable liver cancer. He was given 6 months to live and lived 5 months, dying at the age of 33.

It's impossible to know what might have saved his life, but every day I hope for advancements in hepatitis B and liver cancer prevention care and treatment so no one else has to endure a similar tragic loss. A new hepatitis B vaccine that improves the chance an individual will complete the series will make it more likely that my hope is fulfilled.

In summary, NVHR respectfully urges you to consider this public health and personal perspective.

Thank you.

DR. EDWARDS: Thank you very much.

Joan Block.

MS. BLOCK: Thank you. I'm with the Hepatitis B Foundation, which we established in 1991. It's the only national nonprofit research and disease advocacy organization for hepatitis B. And I just want to let you all know, today is World Hepatitis Day. The WHO designated July 28th as this day because it's the birth date of Dr. Baruch Blumberg, who won the Nobel Prize for his discovery of the hepatitis B virus. Dr. Blumberg also invented the first hepatitis B vaccine, which the FDA itself designated the first anti-cancer vaccine.

As you know, the CDC has said that hepatitis B is the deadliest vaccine-preventable disease, and yet, 50 years later, hepatitis B is still killing almost 1 million people each year.

As a nurse, I have cared for patients dying with liver cancer due to hepatitis B. As co-founder of the Hepatitis B Foundation, I have literally spoken with thousands of patients and families who are living with the burden of hepatitis B. We talk a lot about prevention. The Hepatitis B Foundation is focused on those people who live with the disease every day and lose loved ones every day.

I'm here to urge the FDA Advisory Committee to consider a

2-dose vaccine. The community-based screening programs that we've been doing in greater Philadelphia for the past 10 years has shown us that -- we did a special study 2011 to 2013 funded by the CDC to look at vaccination rates among adults in high-risk communities. We found that only 13% of adults completed the third dose, but 81% completed the second dose. Our finding is not unique; that is something that is found among the 30 other coalitions that we work with across the country conducting community-based screening and vaccination.

We know that if there is a two-dose vaccine, we would be able to save more lives every day, and we really truly could make hepatitis B history.

So thank you.

DR. EDWARDS: Dr. Kim, Ray Kim.

MS. BLOCK: I don't have any financial conflicts.

DR. KIM: Good afternoon. My name is Ray Kim. I'm an adult hepatologist working at Stanford University, and this is my opinion. I'm partially subsidized for this travel today.

As an Asian-American physician practicing in south San Francisco Bay area, I deal with hepatitis B patients every day that struggle with their infection lifelong. And it is important for us to have the right tools to fight the disease burden that is prevalent in Asian population.

I have two points to make: One, as was previously spoken, the adherence for the third dose is very, very, very difficult,

and it is even more difficult when we go out in the community to try to raise awareness and initiate a vaccination program. So having two-dose vaccines will be very important.

In terms of the study, I'd like to point out that the comparison between the two-dose and three-dose studies, if you take that to the real life, the discrepancy between the two study results will be even larger because most of the patients will not get the third dose. So take that into consideration in comparing the efficacy or effectiveness of the vaccine.

The second point that I'd like to make is the prevalence of chronic illness in our population, as was pointed out, there is a lot of patients who need this vaccine later in life with health risks, and those are the very patients in whom the response rate is low. We need a better tool to cover those patients.

And there was a question earlier today about whether we will be -- practicing physicians will be avoiding using Heplisav in patients who have perceived risk, higher risk of having problems. I would argue that will be opposite since the response rate in the current regimen is so low that if this vaccine were to be available to us, we will go to that vaccine for those patients who are expected to have a low response rate.

Thank you.

DR. EDWARDS: Thank you very much.

Dr. Kathleen Schwarz.

DR. SCHWARZ: Thank you. I am a pediatric hepatologist at Johns Hopkins with a particular interest in viral hepatitis. I'm in the hepatitis B research network of NIDDK, and I just retired from being the president of the International Organization of Pediatric Gastroenterologists, where we care for thousands of children with hepatitis B. My travel was supported by Dynavax, but I would've come if not.

So I'd like to emphasize the crying need for having a safe and effective easily administered vaccine particularly for young adults, and this is from my perspective of being in the trenches. I'm a liver transplant doctor, and what's happened with liver transplantation now in America is that one out of four cadaveric livers is a so-called high-risk donor. So these donors have a fairly high prevalence of anti-core antibody and, of course, have a risk of giving hepatitis B to the recipient, but since we have such long waiting lists, we're forced to use them.

My second perspective is from a grant I had to try to improve hepatitis B vaccination of homeless adolescents in Baltimore. I was motivated to apply for this grant from NIAID because we had a 15-year-old, years ago, inner-city Baltimore girl, who presented with fulminant hepatitis B; we had to do a liver transplant on Christmas Eve, and she died several years later of immunosuppression side effects.

So I said this is America, this is a vaccine-preventable disease, this should not be happening, so our grant addressed homeless adolescents. Four percent of them had a vaccine card saying that they'd had hepatitis B vaccine, and with heroic efforts, we did get most of them to accept the baseline vaccine and the 1-month vaccine, but very few to accept the 3-month vaccine.

And then the third is the global perspective from working around the world with pediatric gastroenterologists. We have decided to commit to global hepatitis B vaccine and in part our own experiences, and then the other is the very sobering statistic from Ott et al. that in 2005, a long period after introduction of the hepatitis B vaccine, the number of people around the world with hepatitis B actually grows. So 240 million in 2005 versus 225 million in 1990.

Thank you.

DR. EDWARDS: Thank you very much.

The next speaker will be Dr. Vivian Huang.

DR. HUANG: Hi, I'm Dr. Vivian Huang. I'm from New York City. I work at the New York City Health Department. I am not representing the health department.

But I can tell you that New York City is at the epicenter of the hepatitis B silent epidemic. I can tell you that we have 8.6 million people in New York City, and of those, 3.1 million are immigrants and top countries of people immigrating

from Dominican Republic, China, and Mexico. In New York City we have about approximately greater than 100,000 cases of chronic hepatitis B, which is more than those infected with HIV.

And I can also tell you that of concern since 2013, we've seen an increase in newly reported cases of hepatitis B in New York City. This is very concerning to me, and I don't know why this is happening.

I can also tell you that of the areas where we see high rates of hepatitis B, we are also seeing very low vaccination rates, so those places in Queens and also in Brooklyn, we're seeing about 30% vaccination rate. So clearly, we are failing to vaccinate our New Yorkers and protecting them against hepatitis B.

I can also tell you from the immunization clinic in New York City that we vaccinate over 6,000 -- we've given over 6,000 vaccinations, and of those that have completed is 1,500, so that's 20%, which is another failure.

Another hat that I used to wear, I used to be the hepatitis B director at the Charles B. Wang Community Health Center, and one in eight of our patients have chronic hep-B, 20% of our patients that are pregnant have hep-B, and also one-third of those that we screen are susceptible to hep-B.

The population that we see at our clinic is transient and migrant, and their inability to come back to get their 6-month

hep-B vaccine. They usually can come for their baseline and also their first month.

So I'm urging all of you here to recognize that New York City is a place of immigrants -- 40% are either foreign-born or children of foreign-born -- and we really need a vaccine that can take care of our patients, so I urge you to consider this vaccine.

Thank you.

DR. EDWARDS: Thank you.

Jane Pan.

MS. PAN: Good afternoon. My name is Jane Pan, and I'm with the Hepatitis B Initiative of Washington, D.C. I have no financial tie with Dynavax.

For over 10 years, our grassroots organization is a nonprofit organization and has been providing free hepatitis B education, screening, vaccination, and linkage to care services to at-risk adult communities in the D.C. metro area.

Over the past 10 years, we have provided in-person education to over 18,600 individuals, screened over 11,800. On average, 5% of the population we screen tested positive for hepatitis B and we are linked to -- positive to care. And 37% are vulnerable and needed hepatitis B vaccination.

While we have been successful in educating and screening community members, however, when it comes to vaccination, we have continued to see obstacles. Even when we are able to link

our patients to the first vaccine dosage, it has been difficult to get patients to come back within the 6-month time frame to complete the three vaccine dosages. From our experience and observation on our patients' behavior, we feel that two vaccines over a month regimen may be much easier for adults and could improve their adherence.

Out of the 4,331 patients, about -- that's about 37% of the populations that we have tested over the course of 10 years has needed vaccination. Only 20% have completed three dosages compared to 81% who have completed two dosages.

In closing, we would like the FDA Advisory Committee to consider the risk vulnerable community that includes working immigrants who have difficulties taking time off work to take care of their health. As healthcare providers, you want to seize the moment when we have them in your office or at your site to provide them with services that will also protect the general public's health of a deadly infectious disease such as hepatitis B. We hope that we're providing the valuable information for the Committee to consider.

Thank you very much for your time.

DR. EDWARDS: Thank you.

Nick Walsh.

DR. WALSH: Hi, my name is Dr. Nick Walsh. I'm the Regional Advisor for Viral Hepatitis at the Pan American Health Organization based here in D.C., which is also the regional

office for the Americas for the World Health Organization. My comments relate to the public health implications of the vaccine and the fact that the FDA is a stringent regulatory authority which has influence indirect and direct in other countries around the world. I have no conflicts.

In 2016 the countries of the world, the World Health Assembly, agreed to eliminate viral hepatitis as a public health threat by 2030. This is in line with the Sustainable Development Goals agreed some months before that.

In order to eliminate viral hepatitis as a public health threat, we need all tools at our disposal, both those for prevention vaccine and treatment, of course. We have no cure for hepatitis B. We have effective vaccines, and one is considered today.

Just relating to my brief, which is -- in the Americas, there's 2.8 million people living with hepatitis B. These are people with the infection and potentially could transmit to others. We have 90,000 new infections every year, which is 250 new infections of hepatitis B every day.

We've been successful in immunizing infants, but a big, big gap is poor coverage among adults in the region. We don't have high hepatitis B vaccine coverage among unvaccinated -- among adults at risk of infection. We believe that a shortened duration with less injections to fulfill the vaccine schedule can result in improved coverage.

This is critical right now because we're at the stage where we need to look at the margins, we need to identify the risk groups and increase vaccination rates among these particular risk groups right through the -- right around the region to prevent ongoing transmission if we are to achieve the regional goal, the global goal of the elimination of hepatitis as a public health threat.

Every infection prevented is another one, is another potentially -- another life saved. Each of these people is connected to a family. This is a preventable tragedy, hepatitis B, and I'll finish my comments, then.

Thanks.

DR. EDWARDS: Thank you very much.

Captain James Woody.

DR. WOODY: Good afternoon, I'm Dr. James Woody. I'm a pediatrician and a physician and a scientist. I retired as a U.S. Navy medical officer after 20 years, but I don't speak for the DoD.

By way of background, I have an interest in infectious diseases. My Navy colleagues and I started the National Marrow Donor Program, which you're probably all familiar with. I subsequently developed a drug called infliximab or Remicade, and I serve on the board of the Stanford Children's Hospital-Lucile Packard.

I retired as a captain in the medical corps of the U.S.

Navy. I was a commanding officer of the Navy Medical Research and Development Command. We had Navy research labs around the world. I had previously served as the commanding officer of NAMRU-3 in Cairo, Egypt for 4 years. So we conducted surveys for HIV, hepatitis, Ebola, Congo-Crimean -- and other pathogens worldwide. We saw hepatitis B in over 50% of the populations in all of these places like Sudan and Somalia and Yemen, which you've heard of, but I've been there. Same is true of Afghanistan, Syria, and Iraq.

My command was also tasked with infectious disease surveillance and bio-warfare for the first Gulf War. You may recall, we deployed 500,000 people suddenly over to the Gulf, many of them unimmunized.

So my comment is that the DoD policy of immunizing people is actually very good if you happen to have time. If you don't, it's not going to work. Immunizing people with a third dose at 6 months on a ship with 3- or 4,000 people as you're transporting them is a logistics nightmare; it just won't happen.

So my comment, if you have a combination of vaccine that gets good surveillance and good seropositivity with two doses, maybe in boot camp, that will work and be very, very favorable. And I think their follow-up 40,000 patient review of data going forward, it actually makes a lot of sense. But certainly for the military, short-term vaccination is very, very important.

Thank you very much.

DR. EDWARDS: Thank you, Dr. Woody.

The next is Rhea Racho. Rhea Racho.

(No response.)

DR. EDWARDS: The next is Bunmi Daramaja.

MS. DARAMAJA: Good afternoon, everyone. I want to say thank you to the Advisory Committee for, you know, giving us a courtesy to listen to our concerns.

Today is kind of a memorial day for me and also a day of hope. My dad died from hepatoma today, 1995. He would've been 87 years old. And my brother died from hepatoma. He would have been 50 years old this month. It's kind of a sensitive, you know, month for me when you lose someone that you love from a disease that is preventable. There's so many lives that this monster virus have destroyed all around the world. But in lieu of waiting for a cure, there's -- we have vaccines out there that are saving lives.

I'm here today to speak as a pharmacist and as someone who understands the importance of compliance. The current vaccines we have, have saved lives, but some studies show that an average of 54% of the adults who receive these vaccines complete the series. So why wouldn't we jump hooray when we hear another vaccine out there, you know, that you give two doses within 1 month that will save more lives.

As a pharmacist, one of the great accomplishments that we

have is when you have a patient who is very compliant, you know, with taking their medications. When we give these vaccinations and there are supposed to be three doses and you have to hunt them down, the patients, you know, to complete their series, it's not fun at all; some will not even show up.

I will read some statements from some of the pharmacists that I discussed this with, and one of them said, and I quote --

DR. EDWARDS: I think we need just one more comment and then your time has run out.

MS. DARAMAJA: Okay. One of them said, "I will highly prefer a two-dose that is offered in a shorter amount of time, especially if efficacy is equivalent and covered by insurances. My main reason is compliance issues regarding three doses over a long period of time."

And I thank Dynavax for their effort in making this vaccination to save more lives. It will be a great accomplishment for we pharmacists when we can report that 95% of the patients that we do vaccinate, you know, receive the complete doses.

DR. EDWARDS: Thank you.

MS. DARAMAJA: Thank you very much.

DR. EDWARDS: Thank you very much.

Jason Crum.

(No response.)

DR. EDWARDS: Maureen Kamischke.

MS. KAMISCHKE: Hello. I have no conflicts, and my perspective is personal.

I'm the parent of a child adopted from China. She came to us with hepatitis B. As you know, it's typically a very asymptomatic disease in children, but unfortunately that wasn't the case with my daughter. By the age of 4, she had experienced multiple liver biopsies, treatment with interferon and antivirals and significant liver damage. There was even talk of a liver transplant in her future, but fortunately that never happened.

There's been an effective vaccine, you know, for decades, and of course, we wish our daughter had benefited from a birth dose of the vaccine, but there were other obstacles in our family that we had to deal with. When we came home and learned of her infection, we confirmed immunity of family members only to learn that my husband did not have adequate titers. Grandparents were involved, and they wanted to be ensured that they were protected.

Unfortunately, the currently available vaccines are not as effective in older, overweight, or adults that have any autoimmune issues. The series entails three shots in 6 months to complete, and that really feels like a lifetime when you're worried about exposure to a baby covered in open sores and with a high viral load.

Today my job entails working with people living with chronic hepatitis B. People live with chronic hep-B, they fall in love and they want to live a normal life, and yet, waiting 6 months plus a month or two to confirm immunity is just a little bit too long. Some are not able to generate an immune response even after two complete series, so what are they supposed to do? Marriage proposals are broken, and there's panic and there's shame about their hepatitis B infection.

There are numerous reasons why a current three-shot vaccine series isn't completed and why there are so many that remain unprotected. The availability of a safe and effective two-shot vaccine series, which can be administered within a month, is critical to the elimination of hepatitis B by 2030 in both the U.S. and around the globe.

Thank you.

DR. EDWARDS: Thank you.

The final speaker will be Michael Weir.

MR. WEIR: How are you doing? I have no conflicts. Good afternoon. My name is Mike Weir, Manager for Policy and Legislative Affairs at NASTAD. NASTAD is a leading nonpartisan, nonprofit association that represents public health officials who administer HIV and hepatitis programs in the U.S. and around the world. Our singular mission is to end the intersecting epidemics of HIV, hepatitis, and related conditions. We do this work by strengthening domestic and

global governmental public health through advocacy, capacity building, and social justice.

For many years our members have been concerned about low hepatitis B vaccination rates among adults at risk, including gay and bisexual men, people who inject drugs, and persons living with HIV. As a nation, we must prioritize resources and public health action to ensure that every adult at risk has access to hepatitis B vaccination. We urge the FDA to approve this two-dose vaccine, which will be an important addition to our prevention arsenal.

Public health leaders have identified a variety of reasons for low adult hepatitis B vaccine coverage: low public awareness, clinics not stocking that vaccine or the vaccine, and even concern about losing clients over the lengthy three-dose schedule. FDA approval of a two-dose hepatitis B vaccine will create new attention and awareness of the need for vaccination and ensure a more efficient series completion for providers and consumers.

As the opioid epidemic continues across our country, new cases of hepatitis B and C as well as HIV are emerging. The availability of a two-dose hepatitis B vaccine will help clinicians and public health providers prevent new infections among susceptible adults.

Similarly, the availability of a two-dose vaccine will increase series completion in clinical and public health

settings which serve gay and bisexual men, people living with HIV, and people who inject drugs, the populations experiencing the highest rates of new infections.

The *National Strategy for the Elimination of Hepatitis B and C: Phase Two Report* highlights that we can eliminate hepatitis B in the U.S. The inclusion of a two-dose hepatitis B vaccine will assist in national, state, and local efforts to achieve this goal.

Thank you for your consideration of our comments. Thank you.

DR. EDWARDS: Thank you. Are there any other speakers? Please. Introduce yourself.

DR. YOUNG: Thank you. I'm Dr. Sherri Young from the West Virginia Bureau for Public Health. I have no financial disclosures, and I have no conflicts of interest.

I come here to you from West Virginia today because we are number one in hepatitis B. Not only are we number one in hepatitis B with an incidence of 14.5 per 100,000 patients, we are 15 times the national average as far as hepatitis B incidence in our state. Most of those are identified between the age of 30 to 44, so we do have a heavy burden in our adult population. In addition to that, we do identify multiple risk factors.

Along with the other public health officials that I've heard here today, IV drug abuse is thought to be one of the

biggest risk factors that we have. Again, we're also number one in overdose deaths in the state of West Virginia. So I appreciate you listening to our plight today.

What we are excited about is the fact that we have the availability or potential availability of a two-dose hepatitis B vaccine with good efficacy seen with two doses 4 weeks apart, because that could be used in our syringe exchange programs, it could be used in our harm reduction programs, and it could be used to focus on our adult population so that maybe we will be number one in something other than hepatitis B and drug overdose deaths at some point.

I thank you for listening.

DR. EDWARDS: Thank you very much.

Are there any other speakers for the Open Public Hearing?

(No response.)

DR. EDWARDS: Okay, thank you very much.

So now it's time to go over and address our questions. Do we want to have the questions put on the -- please.

DR. WHARTON: Could I ask if there are any data about the use of this vaccine in persons who had already received one or more doses of one of the currently licensed vaccines?

DR. JANSSEN: No, we haven't systematically studied that. We anticipate looking at that in the postmarketing study.

DR. LEVY: Sorry, another quick question.

DR. EDWARDS: Yes. Please, Ofer.

DR. LEVY: Can Dynavax comment on the manufacture of the Heplisav lots across these studies? Was there any change in the standard operating procedure or quality of the vaccine?

DR. JANSSEN: No, there were no changes in the specs. The vaccine intended for commercial -- for sales is the same vaccine that's been used throughout.

DR. EDWARDS: Yes, Dr. Packer.

DR. PACKER: Yeah, I'm sure everyone knows the answer to this except me, but if someone gets two doses of the currently available vaccine and does not have sufficient titers, does that mean that they are not protected against hepatitis B?

DR. EDWARDS: Probably. I think that the immune response, after three doses, isn't 100%.

DR. PACKER: But I heard at the beginning that after years the serum titers go down and yet there's still protection.

DR. WARD: That's correct, that's correct. That's correct.

DR. EDWARDS: But that's in the face --

DR. WARD: If they had it documented --

DR. EDWARDS: -- response.

DR. WARD: -- serum conversion greater than 10, even if they fall below that in the future, they're considered to be protected in the typical situation outside of immunosuppression.

DR. PACKER: I understand that titers are a surrogate

endpoint, but what I'm trying to figure out is just because someone gets two doses of a conventional vaccine, does that mean they're not protected?

DR. HOOFNAGLE: One issue is whether it's neutralizing immunity or whether it's immunity that prevents chronicity or severe disease, and I'm afraid that's not really answered. But one issue is that people who receive the vaccine may be partially protected, you see. So in long-term follow-up of vaccinated children, for instance, you find evidence of some of them actually became infected with hepatitis B, they develop anti-core, but there's no carrier, right? Am I right, John, on that?

DR. WARD: There's no clinical disease, typically, either. So it's not a sterilizing vaccine.

DR. HOOFNAGLE: It prevents clinical disease.

DR. PACKER: If I only got two doses of the current vaccine and didn't come back for my third, would you say I was okay?

DR. HOOFNAGLE: I wouldn't say it publicly, no.

(Laughter.)

DR. HOOFNAGLE: But this is one question I have --

DR. PACKER: I'm trying to make this --

I'm sorry, I'm trying to make this understandable to the cardiologists.

DR. HOOFNAGLE: Have you used this vaccine to try to boost

titers or try to give it to people who have failed the standard vaccine?

DR. PACKER: I just want to know if the people who have failed the standard vaccine are still at risk of hepatitis B.

DR. WARD: Yes.

DR. EDWARDS: Yes.

DR. HOOFNAGLE: Yes.

DR. PACKER: We know that?

DR. WARD: The proportion that reach that 10 level --

DR. PACKER: I understand. I just want to know if I fall below the 10 level --

DR. WARD: After reaching it.

DR. PACKER: No, no. I never reach it.

DR. WARD: Then you're considered susceptible.

DR. PACKER: Do we have data that says I am?

DR. WARD: In the older studies, yes.

DR. HOOFNAGLE: Very old.

DR. WARD: Very old studies, the original studies, yes.

DR. JANSSEN: So we haven't looked -- again, we haven't looked at current vaccines with respect to Heplisav. If we gave a third dose, we really increase our GMCs a lot, but we haven't systematically looked at after Engerix or after Recombivax.

DR. HOOFNAGLE: So one question is whether after you prime people with this vaccine that turns on your dendritic cells,

you need to give it again or can you get away with the standard alum-induced thing? So the experiment would be is to give --

DR. JANSSEN: Yeah.

DR. HOOFNAGLE: -- as three groups, you understand?

DR. JANSSEN: Right. No, we've never done that study. No. I will say, though, in young people, in people in their 20s, 80% of them had antibody levels over 10 after one dose.

DR. HOOFNAGLE: Have you done the experiment?

DR. JANSSEN: Not the experiment you're talking about.

DR. HOOFNAGLE: You must have done the experiment in mice or something, right?

DR. JANSSEN: No.

DR. HOOFNAGLE: No?

DR. COFFMAN: The experiment to come to --

MR. HOOFNAGLE: One dose of your vaccine and then the second dose with either your vaccine or the standard.

DR. COFFMAN: Actually, I can't think of a situation with any antigen where we've really done that experiment. We've kind of done it the other way around for different antigens, not for hepatitis B, but we've not done it in that order, so I can't answer the question.

DR. EDWARDS: And you haven't done any studies of people who have not responded to other standard hepatitis vaccines?

DR. JANSSEN: Not systematically, no.

DR. EDWARDS: Other questions before we begin to discuss

the specific questions that are addressed? Any context questions or issues that people have that --

(No response.)

DR. EDWARDS: So then let's go ahead and begin to address the questions that we are being asked. The first question is "Do the available data support the safety of Heplisav when administered to adults 18 years and older?"

What I would like to propose is that we go around the table and people discuss their thoughts, and then after we do that, then we will vote on this question.

Yes, Dr. Packer.

DR. PACKER: I didn't want to interrupt. I just wanted to ask, this is a binary question?

DR. EDWARDS: That is -- well, that is a question that we are asked to vote yes or no; however, if we vote yes, we are expected to comment on the pharmacovigilance plan. If we vote no, then we are asked to specify which groups might be included or excluded.

DR. PACKER: But it is possible to vote no --

DR. EDWARDS: Correct.

DR. PACKER: -- and want to comment on the pharmacovigilance plan?

DR. EDWARDS: It's really possible for you to do whatever you'd like.

DR. PACKER: Okay.

(Laughter.)

UNIDENTIFIED SPEAKER: That's embarrassing.

(Laughter.)

DR. EDWARDS: Okay. So let's start, since we have a lot of activity down here, let's start with Dr. Lee, and would you like to comment on your thoughts about the first question, "Do the available data support the safety when administered to adults 18 years and older?"

DR. LEE: Well, from the data, it looks it needs more work, but if it pass, I hope the prospective study will have a better monitor with planned interim analysis with stopping rule to make sure they won't have too much, too many adverse events, like acute MI. And also in the prospective study, like a better, I mean, more detailed time-to-event analysis may be needed, but right now it looks like -- because all the analyses were frequency of the event, so it's difficult for me to make a conclusion. Thank you

DR. EDWARDS: Yes?

(Off microphone question.)

DR. EDWARDS: Please.

DR. DE GRUTTOLA: In the interest of time, the quickest is just to show Slide AA-20, which compares the -- Victor De Gruttola, Department of Biostatistics, Harvard School of Public Health. I've worked in clinical trials for 30 years.

And this slide demonstrates both a contingency table

analysis and time-to-event analysis, which is a hazard ratio from Cox proportional hazards, both types of analyses were done, and as you can see, the 95% confidence intervals and the point estimates themselves are very close and just go -- this slide is looking at the adjudicated MACE in the pooled dataset, and the next slide, 21, presents the analyses for MACE just in HBV-23. And once again, these results are very similar. Analyses were also done just for acute MI, similar results.

DR. LEE: Thank you, Victor. But still, those results for MI are kind of inconclusive.

DR. EDWARDS: Dr. Packer.

DR. PACKER: So actually, I mean, we can talk about this for a very long time but -- and we have, and I guess we could continue. We're not going to know the answer to the myocardial infarction issue. We are just not going to know.

So my difficulty with the question as phrased is do the available data support the safety? And the problem is that that's really not how you decide whether a drug should be made available or not. It's benefit-risk, what do you get versus what the risk is. And so every drug which is presumably on the market has a benefit-risk relationship in someone's favor, and that doesn't mean it is risk free. Every drug on the market has safety issues.

So it's hard to answer a question, "Do the available data support the safety?" Well, the answer is, well, if I asked

that question for every drug, I would say it depends on how pure you want that to be.

My own personal sense is that if the FDA, if this Committee, if the FDA and if the Sponsor agree to put into labeling a description of the imbalance in myocardial infarction events, then that would fully describe the uncertainty that exists, and I would allow a vaccine like this to go forward and would allow people who use the vaccine to at least be aware of what was seen in the clinical trials.

DR. EDWARDS: Thank you.

Dr. Gruber, did you have a comment?

DR. GRUBER: I just wanted to comment, yes. I mean, I think the earlier FDA sort of elaborated that we've had an Advisory Committee where we, you know, asked about would the data support the effectiveness of Heplisav, and the other question was at that time would the available data support the safety? Of course, it is clear that it is always a risk-benefit decision. We would never ask the Committee to only opine on the safety.

But since that question already had been asked in 2012 and today these data were reviewed not only by Dynavax but also by the FDA, you know, we didn't think we had to ask that question over again, and I hope that was clear.

Point well taken, it's always a risk-benefit decision, but I'm also understanding Dr. Packer to say, you know, it depends

what the FDA will write into the labeling, in other words, education, describing this imbalance, etc. Are you saying that you would then go forward and say that available data support the safety in adults 18 years and older?

DR. PACKER: If I could rewrite the question, which I know I can't do, right, but I would -- there's nothing here that allows one to definitively say that there -- you know, there isn't a risk of myocardial infarction; there may be a risk, there may, in fact, be a likely risk, but the question -- I mean, I would favor approving the vaccine as long as what was known about the myocardial infarctions was actually included in the labeling. That way you allow the uncertainty to be fully expressed to the public. I don't understand why we have to reach decisions about certainty when such -- when uncertainty is the only reality. So I would just fully describe the uncertainty.

DR. EDWARDS: Thank you.

Dr. McInnes.

DR. McINNES: So I think this is a very exciting vaccine. It's already been in development for -- and testing for quite some time. The issue about the number of doses is really very attractive. I think the immunogenicity profile is impressive. There are imbalances in ischemic cardiac events in the HBV-23 study. I think despite all good efforts, the causal interpretation remains limited.

The data have been massaged, and I don't mean disingenuously, I mean honestly, as best they can be, and I think we've mined them for what we can get out of them, and they are what they are. I think the analyses that were presented are reasonable, but as somebody who has to now make a decision in myself how I feel about this, I'm left that this really could be a real observation, and I can't come out with a construct to discount that. So this gives me pause.

I am of the opinion that this needs further study. As much as I want to be assured, I'm not comforted by the plans I heard concerning the Kaiser study, and I think it would've been extremely helpful to have understood a little bit more clearly what might be gained from that and how certain we might become in a relatively short period of time, should this be licensed, about what the risk really is.

So those are my comments. Thank you.

DR. EDWARDS: Thank you.

Dr. Levy.

DR. LEVY: I guess I would start by saluting Dynavax because I know they've been at this for a very long time, and you know, we spend most of the time worried about this potential safety signal, this MI, but you know, not only is this adjuvanted vaccine effective, it's super-effective. I mean, if you look at the data compared to the vaccine we have now, it's not even close. This thing blows it out of the

water. And the number of dose issue is huge, and getting strong immune responses in older individuals is huge. Vaccinal antigens tend to be expensive, so if you can have an adjuvant -- so for a lot of reasons, I'm very excited about this vaccine.

I'll try not to rehash what other people have said. It's hard to exclude that there's some signal there for MI, and I think this should move forward, but any way it moves forward, there needs to be some sort of evaluation that that's meticulous with some sort of design that allows a rapid identification of a signal if it's verified.

So I think most of the data we saw did support safety, but that one piece that all the committee members thus far have commented on is the unknown, and now the question in front of us is what is a rational way to follow up on that in a responsible and meticulous way without throwing the baby out with the bathwater?

DR. EDWARDS: Thank you.

Dr. Kotloff.

DR. KOTLOFF: Well, it's interesting. I think a very consistent picture is coming through, and I pretty much am in line with the comments that I've heard. I think that there is a place for this vaccine. It has very impressive performance in generating high antibody levels after fewer doses, but I think that we haven't heard convincing evidence that there

isn't convincing evidence yet that it might not be associated with myocardial infarction and also with rare autoimmune events. I think both of those issues are in play.

I think that doing post-licensure surveillance and doing an adequate job at trying to sort this out post-licensure will be extremely difficult, for one, because the risk group that we're worried about may -- will be hard to do the study in that group. And two, the problem with the existing vaccines is that people aren't compliant, and to do a really good study you need to have a fair amount of compliance. But I think that there should be a lot of attention in trying to develop a very good postmarketing vaccine plan.

Thanks.

DR. EDWARDS: Dr. Sawyer.

DR. SAWYER: I will echo the previous comments, including the one that answering this binary question is a challenge. I think, though, that there is a reasonable chance that this myocardial infarction signal is spurious based on the multiple variables that were looked for and the lack of a temporal association that we've gone over.

So I do think the benefit outweighs the current assessment of the risk, but as I'm sure we'll discuss in a minute in the subsequent questions, I, too, am very concerned about the design of the postmarketing study. It needs to be able to answer the question, and it needs to be able to answer it

quickly, and I think as proposed, it might not do that.

DR. EDWARDS: Thank you.

Dr. Portnoy, would you like to comment on this question?

DR. PORTNOY: I would, thank you. Can you hear me okay?

DR. EDWARDS: Yes, very well. Thank you.

DR. PORTNOY: Thank you. And thank you for letting me participate in this event by telephone. I had surgery 2 weeks ago, and my doctor didn't want me to travel, so thank you for accommodating that.

I would vote yes on this question. I think that the safety of the data are reassuring. The company has clearly addressed the issues that were raised in the previous submission.

In my opinion, part of the safety includes the fact that it is extremely effective. I think it's not safe to be at risk of getting hepatitis B. It's safer to get the vaccine than to be at risk of hepatitis B, so the risk-benefit is what I look at. The improved schedule will also improve compliance.

My only concern, of course, is the signal that we've all talked about for the cardiovascular events such as MI. I suggest that the package insert include a warning or some kind of alert for individuals who have increased cardiovascular risk factors. Perhaps increased attention should be paid to those individuals, or perhaps they should be instructed to get the other vaccine.

The immunologic and autoimmune adverse events don't seem to be greater than -- with the new product than with other vaccines. All vaccines seem to have at least a minor risk of having those problems, so I'm not overly concerned about those.

Basically, I just don't think it would be right to withhold this vaccine from the millions of people who could benefit with it because some people have risk factors for MI. Those people could be managed in a more specific approach.

The proposed surveillance program is good, though as everyone has mentioned, I'm not convinced that the patients will be allocated in an unbiased manner. Patients with cardiovascular issues might be just sent to a different clinic to get the other vaccine perhaps. I suggest asking the medical community in general, the whole national community, to be more vigilant in reporting any AEs that might occur in association with the vaccine, perhaps through marketing materials that the company puts out when they promote this vaccine. There should also be instructions on how to actually report an AE because not all physicians know how to do that. When the reports come in, the FDA should probably pay closer attention to those particular reports.

So those are my thoughts.

DR. EDWARDS: Thank you very much.

I'm Kathy Edwards. I agree that this is difficult to address in yes or no. The available data that do exist have

been looked at in very meticulous and comprehensive ways and have been thought about and really dissected in an admirable way, but certainly as Dr. Packer said, it still does leave questions. But as Mark said, it does also suggest that maybe it is spurious, and so I think it is very confusing indeed.

I think the impact of a two-dose schedule, particularly with this potent adjuvant, would immunize effectively many more people than we are currently. However, I am pretty dismayed about the proposed pharmacovigilance plan, and I think it needs to be more comprehensive, I think it needs to think about how patients will be allocated, how patients will be followed, how the vaccine will be distributed, whether it will only be able to be accomplished in one setting and really needs to -- a lot more information and details to allow me to feel comfortable with a yes.

DR. GRIFFIN: Yeah, so --

DR. EDWARDS: Dr. Griffin.

DR. GRIFFIN: Thanks. So I'm going to vote yes. I'm comfortable that the study really addressed the concerns of the 2012 Committee adequately, that HBV-23, I thought, laid some of those concerns -- much lower level. There's this new concern about MI, but I think that was unanticipated.

I don't think -- usually, you can find good biologic plausibility for just about anything, but I think the temporal association, the biologic plausibility for this association, is

not strong.

I think if we spend a lot of time on the prostate cancer and -- where we saw the very opposite thing, you know, if things were different, we might be very concerned about prostate cancer in Engerix.

So I think it's, you know, no one knows obviously, and we won't get an answer. And like everyone else, I think the postmarketing study will be very important not only for this vaccine but for the adjuvant and for using it going forward, especially in people who are at risk for -- elderly people who are all going to be at risk for cardiovascular events. So I'm not sure we want it to be something where it's set up so that people at risk for cardiovascular events are excluded.

DR. WHARTON: So I think probably everything I'm going to say somebody else has already said. It's very exciting to have a vaccine with these characteristics at this point in development, and it seems to me that the available data allow it to move forward.

That doesn't mean that all of the issues have been fully addressed. Clearly, there was this unanticipated imbalance around acute myocardial infarction, which, you know, really didn't make any sense based on earlier experience or what we think about how the components of this vaccine work and what we understand about how myocardial infarctions happen and the timing, where are really -- the divergence was a 100 days out,

and it's hard to put all that together in any way that raises a higher level of concern.

So I think it's something that can't be dismissed, it has to be addressed. My own feeling is it can be addressed post-licensure. I have not heard enough about the post-licensure plans to make me confident that right now there is a plan that will fully do that, but I believe that plan can be developed. I just don't know that it has been yet. And clearly, post-licensure surveillance is going to be important for the kind of rare autoimmune conditions that cannot be ruled out that we still might see post-licensure with wide disparate use of the vaccine.

So I will vote yes when the time comes to hit the button, but there clearly will need to be additional work done.

DR. EDWARDS: Dr. Monto.

DR. MONTO: I'm not going to repeat all of the wise words that we've heard. My initial reaction when I saw the results in reviewing the material was that this was spurious because we -- those of us who do studies always worry about something like that coming up, but I wish it were not so spurious, so unbalanced. I mean, I think that's what's troubling. The results really were very unbalanced, and the probability of that happening is a bit of a worry.

I'm a bit uncomfortable in voting in the order that we're voting because I would be comfortable given the superiority,

and I know it's -- this was not a superiority endpoint. In voting, I would be much more comfortable voting yes if I knew what the pharmacovigilance study was and that it would not result in the kind of label that would result in nonuse in just the populations where it should be used, and that's my major concern.

I think this is a vaccine we want to see used, and I think we need to take into consideration whether voting yes and then talking about pharmacovigilance is better than voting no and then approving for a specific population, which is the other question and one I ask for guidance on. And I think we really need to choose between two not-too-comfortable decisions.

DR. EDWARDS: Ruth. I think we need to finish before -- thank you.

DR. LYNFIELD: I guess, whether it's an advantage or disadvantage sitting at this end of the table, I think everything's been said. I agree particularly with the last few speakers. I do think that it probably is spurious; I think that it would be very important to have a very robust pharmacovigilance plan, as people have articulated, and perhaps after we go around the table, could we talk a bit in greater detail, I think that would be very useful, about what that pharmacovigilance plan would be?

But, you know, again, as everyone said, it's a very exciting vaccine and, you know, let's keep an eye on the big

picture and the lives that we can save.

DR. EDWARDS: Dr. Englund.

DR. ENGLUND: Yes. I would just like to say I agree. I think this is an important vaccine. I work in the field of transplantation. We need this vaccine to save lives, and we can't wait 10 years to get something like this. I truly feel we need it, we need it.

I think we have to judge this as a risk versus benefit and there is the imbalance of MI, which may or may not be real, and there's an imbalance of seroprotection, which people who get infected with hepatitis B have incredibly high rates of serious disease and even fatal disease.

So I am very much in favor of this, and I think the FDA has a history of helping design postmarketing trials, and they know how to do that, and we should empower them. We can give them ideas, but we should empower them that that should be part of the deal.

DR. EDWARDS: Thank you.

Dr. Bennink.

DR. BENNINK: Yeah, I'll try to keep it short because I think great comments have been made. But I think in terms of the postmarket, we don't know all the details. But I still think I would be more in favor, even though I know it's difficult, in addition to whatever they were doing there, to do something that was more targeted toward the myocardial risk

group and try -- even if it's small or something like this, and try to prospectively really follow them in some way that may tell you that there's risk coming in before they, in some respects, even have problems or before it really becomes death or something like this. So I would say along that line, you know, we don't know; it may be spurious, it may be something else.

I would also make a little bit of a comment that I think Dr. Packer made the comment, that atherosclerosis is inflammation, and therefore even though it's different than what we typically think of, and maybe this is because innate immunity is becoming so much more studied and everything else, it is immune mediated, from that perspective. It's not what you're thinking about in terms of autoimmunity or something else, but it is immune mediated.

DR. EDWARDS: Dr. Hoofnagle.

DR. HOOFNAGLE: Yes, well, I agree that this is a real advance for hepatitis B. It's something that's been defined in the past as a great need, a better vaccine, more potent, and also given in fewer doses, so that's completely clear.

The problem here is that we're not really dealing with approval of a hepatitis B vaccine so much as approval of an adjuvant. A new adjuvant, as I understand, would be the first in human use approved. So that's really the issue; that's where the safety comes up.

But that puts a greater burden on you because this is not going to be the last use of adjuvants that interact with the toll-like receptors; I suspect more and more are going to come. So that's why I think it's very critical that this issue be addressed directly and answered. And so I would vote yes for this vaccine.

But I'd also ask the FDA to basically request a study specifically focused on myocardial infarction. If you do another big study of 20,000, 40,000 people, something else is going to show up as different between the groups. This time it will be breast cancer or something worse. But I think this, what's been found so far, really needs to be addressed directly and maybe in a focused study rather than a global study.

DR. EDWARDS: Thank you.

Dr. Ward.

DR. WARD: Thank you. Well, as a member of the Committee, I just wanted to verify and second a lot of the comments that have been made by the Sponsors or by the members of the audience regarding the public health need for this vaccine and how we do have to balance benefits and risk.

You know, as was mentioned, we do have a problem with incidence of new hepatitis B infections in this country. They're among older adults who are -- immunosenescence is a real problem with the current vaccines, and they happen among populations where a three-dose schedule is really problematic.

We've heard some data from both of those audiences about the problems going from the second to the third dose.

The other issue is about when vaccine series is not started at all because of the complexity of that three-dose series for those settings where these marginalized populations are at highest risk for hepatitis B or are getting care when they do access the healthcare system. So there's a strong public health need for this type of vaccine, I think, that can be filled by this hepatitis B vaccine, but it has to be a safe vaccine.

And I think, you know, when looking over the data and hearing the presentations, I think the questions that were raised about safety in the original studies had been adequately addressed, and I think those questions were resolved in the complete databases we've heard from the FDA presentation. And it's a very large number of study subjects when you look at all of those studies collectively.

The acute myocardial infarction, you know, was an unexpected finding; it was not the intent of the study to look at that question. I think the temporal association is really weak, and so I think it is an issue of concern which should not preclude the licensure of this vaccine.

So I think the vaccine data collectively demonstrate that this vaccine is safe enough to be licensed for use, and then we can have a discussion about whether we want to have any

populations of concern to be highlighted in the package insert and what are the proper designs of postmarketing surveillance after licensure.

Thank you.

DR. EDWARDS: Thank you.

Dr. Nolte.

DR. NOLTE: I don't have any comments.

DR. EDWARDS: Yes, Dr. Levy.

DR. LEVY: Yes. So something that Dr. Hoofnagle said kind of resonated with me and made me think of a very broad public health reason that it would be important as this moves forward to really nail a clear answer on the MI front, and that is that, you know, however this moves forward, and I hope it does, that FDA will have to consider that even if the association is spurious and even if postmarketing suggests that it's spurious, the better that point can be nailed down, the better it is for public health because what we don't want is a situation where there are a lot of vaccines in the world and a lot of myocardial infarctions in the world and there's a public perception of an associated risk.

Vaccines already, as you know, have suffered from inappropriate conclusions about autism, and the last thing the whole field needs is for elderly individuals -- so I just want to amplify what Dr. Hoofnagle said, that any postmarketing plan should be extremely rigorous to nail down that point.

DR. EDWARDS: Dr. Gruber, I wanted to bring up the question that Dr. Monto asked because it is -- if one answers yes to the first question, then that means for all populations, correct? Or do we -- go ahead.

DR. GRUBER: If the Committee were to answer yes for the first question, that would mean that that would be an indication in adults 18 years and older, that's what the indication would read, yes. If there -- well, I'm good at this. Yeah.

DR. EDWARDS: So in some ways it might be easier if we sort of incorporate Question 1 and 3; is that possible? Because we could say, you know, yes, we agree for all or no, we agree for all except this. But I'm happy to go as it's written, if that's how you prefer.

DR. GRUBER: Well, I'd like to make a point that the indication that the company seeks is really active immunization against, you know, infection in adults 18 years and older. That's the indication they would like to have in the package insert, and this is how we phrased the question. I very much hesitate to really reverse the sequence of the -- you know, of what we're asking here.

DR. EDWARDS: Good. Thank you for your clarity.

Okay, are there any more questions about or comments that people want to make about this first question? Yes, Dr. Monto.

DR. MONTO: You had mentioned having more discussion

before we vote about the pharmacovigilance because I think that's the thing that gives us some hesitation. The idea that we're not going to know for maybe 2½ years of use what the answer is about safety and the MI question gives you a little pause given the fact that there will be a move to use this in the population that needs it most. And if this doesn't happen, I've seen other situations where if there are questions involved when something new is launched, this just sort of lives with the product forever.

DR. EDWARDS: So I think that we do need to vote on the first question yes or no, but then I think we need to -- if yes, then I think that we will need to comment on the pharmacovigilance plan after a yes or no vote.

Yes?

DR. MONTO: We can't reverse that order?

DR. EDWARDS: Those are not the instructions that we received.

DR. MONTO: Okay.

DR. BENNINK: But could you -- excuse me. But could you -- if Arnold wants to discuss what those plans would be without any votes, what the committee members are thinking about a plan, the discussion about those plans, I mean, you don't think we should discuss those at all until there's a decision about 1?

DR. EDWARDS: I'm fine to hear other ideas or plans about

it.

Dr. Gruber, do you want us to do 1, or could we open the comments on the plan for 2? Would you prefer just to have us vote for 1 and then go on to 2 and 3 and 4?

DR. GRUBER: Well, I'd like to ask a question. Depending on the discussion of the pharmacovigilance, what I'm hearing is that somehow would influence how you vote on Question 1?

DR. BENNINK: Well, for some of the people who commented, that was my impression, that people wanted to hear about a robust pharmacovigilance plan.

DR. GRUBER: Right, but wouldn't you have the chance to comment on this when we discuss Number 2, "Comment on the proposed pharmacovigilance plan"? I mean, we put that point here for a reason because we, you know -- we agree that, you know, we have to have a robust discussion and really seek your input on what you heard today on the PVP and what you would like to see.

DR. SAWYER: I think what some of us would benefit from is clarification on the ability of FDA to work with the manufacturer on the details and to what extent can you dictate what is in the postmarketing study.

DR. MONTO: And particularly the timeline.

DR. LEVY: I guess, Dr. Gruber, our question is, does FDA have the power to make the approval contingent on a particular plan?

DR. GRUBER: We certainly, you know, have -- you know, can discuss or can request, you know, the pharmacovigilance plans to have certain elements, and we can also, you know, discuss -- well, we have the authority to make it a required study versus, you know, a follow-up safety study; in other words, a postmarketing commitment versus a postmarketing requirement so that we can do -- but there is -- I mean, I think what I'm hearing, this is even a bit more complex. It's like what systems do we have in place to really, you know, look at this event versus what can the company do. I think we would have to have these discussions in particular, you know, if the Committee were to say we need to request, as was expressed by one of the committee members, we need to request for, you know, for the company to look specifically at the MI event.

So I think we have the authority to request, you know, for certain studies to be done, but I think it also depends, again, you know, what can we do given our existing systems and what the company will be able to do.

So I think we would have to have much more discussions, and I very much hesitate, really, here on the spot to tell you really yes or no, this can be done, this cannot be done. I invite, perhaps, my colleagues from the Office of Biostatistics and Epidemiology to weigh in here, if somebody wants to further elaborate on that.

(Off microphone response.)

DR. GRUBER: Yes, sure.

DR. EDWARDS: Dr. Sun.

DR. SUN: Hi, this is Wellington Sun. I'd just like to follow up Marion and maybe expand a little bit.

FDA has the authority to require certain types of postmarketing studies, and the process in which we do that is based on our interpretation of the data and working with the manufacturer to design the best study possible.

Now, I think there are limitations to what we can do even with the best of intentions, and that is the nature of postmarketing studies; for example, sometimes it's difficult to do a randomized controlled study at postmarketing.

So I think we have to recognize the feasibility of those types of studies in deciding, and that's one of the reasons why I think looking at studies, whether they're pre-licensure or post-licensure, is really important because the nature of those studies could be determined by whether it's a licensed product or pre-licensure. So I just want to sort of clarify that.

DR. EDWARDS: Dr. Kotloff and then Dr. Hoofnagle.

DR. KOTLOFF: I'm wondering whether our recommendation can include certain elements about the postmarketing surveillance. I don't think that we can design, here and now, a study that would be robust and satisfy it, but there could be certain elements, for example, that a study is required, that a study is designed that minimizes bias by doing appropriate allocation

to the two groups to examine the factors that we're concerned about, the events that we're concerned about, that the results be made available before 3 years' time, you know, within a certain time frame. So if we could just address what we think are the key elements.

DR. EDWARDS: Well, certainly that is -- 4 is a question that we're being asked, what additional studies are needed, so I think that we can address this.

Dr. Hoofnagle.

DR. HOOFNAGLE: Well, once a vaccine is made available, its use will depend on its cost, we haven't talked about that, and its perception of its safety, and if this vaccine is licensed with a big warning on it, this is a chance for them to erase that warning, is to do a study to show that that was -- it was just happenstance, and with a critical prospective study this difference doesn't show up. So that's one way that the FDA has great influence on postmarketing studies: your product label.

DR. EDWARDS: Any other comments?

(No response.)

DR. EDWARDS: Okay, so we are being asked to vote yes or no, "Do the available data support the safety of Heplisav when administered to adults 18 years and older?" So a yes is a plus, a zero is an abstain, and a minus is a no. Vote now.

(Committee vote.)

DR. PORTNOY: And I e-mailed my vote to you already.

DR. EDWARDS: Could you also give a verbal vote, please?

DR. PORTNOY: Oh, I vote yes.

DR. EDWARDS: Please show the vote.

(Pause.)

DR. EDWARDS: They'd like us all to vote again, right? Okay. Vote again, just like in Chicago, right?

(Committee vote.)

DR. PORTNOY: And again, I vote yes.

(Laughter.)

DR. EDWARDS: Eleven yeses, three abstains, and one no.

Okay, let's move now to -- oh. Okay, all right.

For the record, then, we want to vote -- to name the individual people who have voted for what -- so the greens or the yeses are Ward, Hoofnagle, Bennink, Englund, Lynfield, Monto, Wharton, Griffin, Edwards, Sawyer, and Kotloff.

Okay, there are three abstains, right? Three, let's see. And those are Levy, Packer, and Lee.

And McInnes, no.

Okay, so we'll now go to the second question: "Please comment on the proposed pharmacovigilance plan."

Dr. Lee, would you like to start, please?

DR. LEE: Yes. As we discussed earlier, it would be good to have a better plan to study -- for the prospective cohort study to include a different age group because, first, I'd like

to say, actually, I am for the approval of the -- of this vaccine. I'm not against it. Just as a statistician, I think the safety was not -- was inconclusive. But for the pharmacovigilance, the plan, I think it would be good to have, like, a specific subgroup analysis for the MI and also for other ratio study.

Thank you.

DR. EDWARDS: Okay.

Pam, do you want to go ahead, and then we'll get Dr. Packer --

DR. McINNES: No, given my vote, I would rather not go ahead.

DR. EDWARDS: Okay. Okay, good.

All right, Ofer.

DR. LEVY: We're asked to comment on the proposed --

DR. EDWARDS: Pharmacovigilance plan, yes.

DR. LEVY: Right. You know, I already did that several times.

DR. EDWARDS: Okay.

DR. LEVY: So, you know, I guess my question to FDA is then FDA does have the authority, Marion, to put the label, to put a label -- is that something that's been done in the past in this kind of setting?

DR. GRUBER: I mean, first of all, if safety events have been observed and it's regardless on what study or what vaccine

this is, we can, you know, describe those in labeling. But, in addition, we also have the authority to request certain postmarketing studies. We can -- you know, these PMR, postmarketing required studies, they, if you will, hold the company to a higher standard so that these studies need to be done, they need to be conducted. Postmarketing commitments are also studies that can be done, but it is more -- it's more like general additional safety data that need to be gathered.

So what this is going to be, I don't want to really decide here at the table, but we have the authority to request one or the other, okay? And that's contingent on some other issues, you know, prescribed by law, such as we have our own system, for instance, the Sentinel system. If we're not able to do these type of studies using that system, then it falls on the company to do, you know, a PMR. But yeah.

DR. EDWARDS: Karen, do you have any additional things that you haven't commented on about the proposed pharmacovigilance plan?

DR. KOTLOFF: I guess just a few specifics. One is that if the study were done at multiple sites, that you could have faster accrual and a quicker answer, that that would be an approach that I would think about. And then adequately powered for the age group at risk for MI. And then using the Sentinel surveillance systems for more longer-term surveillance looking at autoimmune. I think that's outside of what the company is

expected to do but what our existing systems might do.

DR. EDWARDS: Mark.

DR. SAWYER: Well, I think several people have articulated how important it is to understand this myocardial infarction connection, so I would suggest that whatever study be done is required, not just a commitment from the company. I think just letting it happen in Kaiser is fraught with some concerns about the age group that would be immunized and whether the Kaiser physicians would skew the use of the vaccine based on what is currently now public record about myocardial infarction. So I think a more scripted study is going to be required, and I would leave it to the FDA and the company to come up with what that looks like.

DR. EDWARDS: Dr. Packer, since you abstained, you really don't have to comment on the proposed pharmacovigilance plan, but we would welcome if you have comments.

DR. PACKER: The Sponsor has actually come up with a brilliant plan for such a study, which would be a cluster randomization at Kaiser. Essentially, certain Kaiser colleagues would only use one vaccine versus another on an exclusive basis. The actual assignment of that would be random.

The result of that would be a very low likelihood of major confounding, and it would make for an interpretable study that could go very, very quickly. If it's just a usual prospective

cohort study with choices being made, I think it's going to be -- they're going to get data which is going to be hard to interpret.

DR. EDWARDS: I think my comments about the proposed pharmacovigilance study, I already made several. I do think a couple things are really important. One is timeliness, so that if indeed we are concerned about this, and we are, then we want to make sure that we address this in as expeditious of a manner as possible, as Karen said, perhaps having many centers.

I think also the ability to look at, in a concentrated way, some of these patients using perhaps biomarkers or other sensitive assessments of cardiovascular function may also be helpful after the licensure as well, so I think that more detail about that as well.

Dr. Griffin.

DR. GRIFFIN: Yeah. I would agree that it should be a requirement rather than a commitment, and I mean, it would actually be more like a retrospective study if it was done as described unless someone collected data prospectively. There's data already in the EHR, but that's not considered a prospective study.

So I think the Sponsor and FDA might consider thinking about collecting cardiovascular risk factors prospectively to people who are getting both vaccines, so just to get a better level of detail for the analysis.

DR. EDWARDS: Dr. Wharton.

DR. WHARTON: The only additional comment I have is that consideration of an interim analysis plan that would allow either more timely reassurance or more timely identification of risk if they're identified.

DR. EDWARDS: Thank you.

Dr. Monto.

DR. MONTO: I certainly don't have any problems with observational studies since that's what we are mainly involved in right now. But I think my concern is the timeliness and the appropriate use of the vaccine in the populations in which you are most likely to see the events and given -- also, reliance on one area of the country and one health entity is sometimes a little risky. So if something else could be done, that would be, to me, helpful. And I think the timeliness is what is really going to be important because you just want to set this to rest as quickly as possible.

DR. EDWARDS: Dr. Lynfield.

DR. LYNFIELD: I agree with the comments that my colleagues have just made.

DR. EDWARDS: Dr. Englund.

DR. ENGLUND: I agree, too. I would like to just amplify two little things. When risk is mentioned, I really think that we need to be having an age limit or something. If we could design this -- I don't want to see 20,000 people between 20 and

40. I want to see 20,000 people between, you know, 50 and 70 or 40 and 70.

So I really think -- I know that we've talked about cardiac risk, but really, if you just -- looking at the data they have, if you just did age risk, you really would be enriching for that population, and that's number one.

And number two, the comment was raised in the audience, and I noticed it when I was looking at it, is the Asian population is really minimal. This is, you know, 1 or 2%. It's really unfortunate, and I really -- we see this time and time again. The Sponsor should take this into account, when they design studies, that we should try the vaccine in the population it's going to be designed for. But California is a good place to do that so we can enhance the Asian population.

Thank you.

DR. EDWARDS: Dr. Bennink.

DR. BENNINK: Yeah, I guess I'm still thinking along the same line that I spoke on because I think a lot of the other -- it does -- the larger study, which I think it would be good and everything, still seems more retrospective in some ways. You're going to say the incidence or whatever you've got during these things, and I'd rather, in addition or something, have a subset that really focused on this but was really looking at them, you know, as they were going and not waiting for an infarction to happen, okay, to see whether you were actually

getting, you know, something more happened, as you say biomarkers or whatever, noninvasive scanning or whatever you have.

But even if it's a smaller subset, you're kind of looking at that and trying to see if there isn't a trend or something here or if it is really a spurious result and there's nothing there.

DR. EDWARDS: Thank you.

Dr. Hoofnagle?

(Off microphone response.)

DR. EDWARDS: Okay. Dr. Ward.

DR. WARD: No, I think most of what's been said and, you know, the guiding principles are get the population and the surveillance at the greatest risk for this adverse event and make sure the surveillance catchment is of sufficient size to really look at the question accurately, and then monitor the data as timely as possible that we -- so that we can confirm or refute the safety concern as quickly as possible and to communicate that information as soon as possible.

Thank you.

DR. EDWARDS: Dr. Nolte, do you have a comment?

DR. NOLTE: I have no comment.

DR. EDWARDS: Thank you.

Yes, Dr. Packer.

DR. PACKER: Yeah, I just want to say that 40 to 60 is

actually not the age range for myocardial infarction; it's older than that and just -- if we see patients with an MI who are in their 40s and 50s, we consider that to be highly unusual. This is a disease in an older population.

DR. HOOFNAGLE: Could I ask a question of Dr. Packer? You mentioned that there are some instances where the MACE doesn't work, that it's a specific diagnosis, it's different than the rest. Can you give us an example of that?

DR. PACKER: Yes. The data originally on rosiglitazone was an MI signal only, no stroke. The original data on COX-2 inhibitors was in myocardial infarction signal. There was a minor stroke signal. So you can have these imbalances. Please understand that the only reason that myocardial infarction and stroke are combined is largely because of a platelet combination as opposed to an inflammatory combination. Plaque rupture is not -- is the way that myocardial infarctions occur, but it's not the way, or the primary way, that stokes occur.

DR. HOOFNAGLE: But weren't both of those examples maybe not correct?

DR. PACKER: The COX-2 inhibitor example is unbelievably correct. That's why we only have one of them on the market.

DR. EDWARDS: Pam, do you want to comment on whether -- a more specific subpopulation you would be more comfortable with?

DR. McINNES: I'm struck by looking at the population in which Dynavax so bravely ventured, and I think it is brave.

It's an incredibly unhealthy group of people. When I look at, you know, the BMI, the diabetes, the cardiac disease, the drug abuse, the yada, yada, yada, yada, it just goes on and on and on, and maybe it's a miracle you didn't find more problems than this.

So I think this is the problem because we're used to thinking about, you know, relatively healthy, pure populations in which we introduce -- certainly in pediatrics that's what we're used to thinking about.

And so here you've got this conundrum, and now you've got a signal, and is it can you construct somewhat in order to launch this and get maybe additional studies to help you broaden that population? Or, in fact, does that strategically present problems in the long haul? And we have examples of a pediatric vaccine that struggled with that very same issue. Never quite had the data for the younger population, launched with an older, and probably never recovered.

So I would have to -- I don't think I have anything very intelligent to say about this, this afternoon. I have to think a lot more about it now that I'm no longer thinking about the whole pool. I think there are perhaps -- if you're seeking an indication for 18 and older, I don't dismiss the younger population. I think that's your indication you're seeking, and I think your signals won't be there, and I think it's a much easier way to go. Are they the population that particularly

need this vaccine? Probably not. So that's the yin and the yang of that one.

That's really where I am at this point. I am going to think more about it. I'm worried about the Asian data. When I looked at it, I thought it was regrettable that there was not a bigger body of data in Asians because of the burden of disease that is pouring in.

DR. EDWARDS: So in terms of the Question 3, we've sort of -- I'm not sure we need -- we've sort of addressed that.

DR. GRUBER: You know, we just had some sidebar conversation and e-mailed the FDA on really where to take this given the vote: 11 yes, 1 no. But we still felt, you know, we had three members that abstained. It will be great if those three members could opine, at least, on Question 3, okay? I don't think it's necessary to really turn it into a yes/no vote, but the issue about "Do the presented data support usage in a more specific subpopulation," given that these three members didn't vote yea or nay, I think it's -- I would really like to hear them elaborate on that a bit.

DR. EDWARDS: So Dr. Lee, Dr. Packer, and Dr. Levy could comment on that. Yes?

DR. BENNICK: A comment.

DR. EDWARDS: Jack.

DR. BENNINK: Pam, in terms of what you said, though, in a sense, the risk-benefit ratio is greater in that population

that has the most risk as well. Wouldn't you think that that's true?

DR. McINNES: Jack, I wish it just -- that's never how it plays out in vaccines. Okay, we don't intellectually sit there and say, oh, the benefit is this and the risk -- it's not how it happens; you get hammered. When it doesn't work out right, you get hammered. So I'm concerned. I'd say yes, intellectually that makes a lot of sense. Does it work that way? It doesn't work that way. So it concerns me.

DR. EDWARDS: Okay, so Dr. Lee, are there any more specific subpopulations that you would support usage in?

DR. LEE: From the efficacy study, it seems that this vaccine is used for, for population except the older age, so that's just my concern. Yeah, okay.

DR. EDWARDS: So age, the older age would be one that you would be more concerned about? Okay.

DR. LEE: Right.

DR. EDWARDS: Okay, Dr. Packer.

DR. PACKER: Actually, I think it would be self-defeating to restrict this to a subpopulation because if you want to do a postmarketing study and you want to get the answer, you would like to get the answer in a high-risk population, which means that the vaccine has to be available to a high-risk population. So if you really want to get an answer about myocardial infarction, you have to allow the vaccine to be used in high-

risk people.

DR. EDWARDS: Dr. Levy.

DR. LEVY: Yeah, I agree with Dr. Packer.

DR. EDWARDS: Dr. Sun, did you have a comment?

DR. SUN: Yeah, I just want to make a comment to Dr. Packer's points. I think when we framed this question originally, it was a measure to mitigate the risk, it's going back to risk-benefit, and we were thinking that if the signal were reopened, how we might -- might we mitigate that risk and still allow the vaccine to go forward and that was -- that's the reason why we are asking the question that is -- we had examples in vaccines where we approved an indication, age, and usage in a limited number and then extend that by further studies when the vaccine is licensed.

DR. PACKER: Maybe I can just quickly -- there's actually only one risk here, and that risk -- and it's a really horrible risk -- is that 3 years from now you still won't know the answer. That's the risk you don't want to take.

DR. LEVY: Yeah. And I want to echo that, and that's why a lot of the panelists kept harping on having an excellent postmarketing plan, because the worst outcome would be to have a muddle and we still don't know, and the public starts picking up on this and there are all sorts of concerns. So that's why having real clarity from the FDA -- and I know Marion has spoken to this, but that's why we keep coming back to this

point, how rigorous can it be at the postmarketing level, and are your statisticians satisfied that you'll have, within a year or a year and a half, you know, a clear answer. That's critical, right?

DR. EDWARDS: Dr. Lee.

DR. LEE: Yes. My original comment was -- I meant to say that I suggest the approval of the use of the vaccine, but with post-license studies emphasized, with emphasis on the older people because they're -- they may have higher incidence, yeah.

DR. EDWARDS: Okay. So the fourth question, then, is "What additional studies (either pre- or post-licensure) are needed to further evaluate the safety in the general adult population or in specific subpopulations?"

We've sort of beaten this horse quite mercilessly. Are there any other thoughts or comments about additional studies that we haven't commented on?

John.

DR. WARD: I don't know when certain populations like pregnant women, you know, get brought up, but it seems like there are certain populations that are always of a concern about vaccination. I know just the recommendation for the use of the current hep-B vaccinations were just -- just in the last, you know, 10 years were -- you know, there was a recommendation that you could vaccinate pregnant women. And so maybe that will be by extension you can use this one as well,

but that is one population that there's always a safety concern about.

DR. EDWARDS: So I think that there is a registry for pregnant women that is proposed, but it would not be a vaccine recommended for pregnant women.

Yeah, Jan.

DR. ENGLUND: I really think, and it was brought up in the comment period, but adolescents are a high-risk group, and it would really -- I know this is going down to 18, but if we could get a vaccine like this down to 16, that adolescent population is a high-risk vulnerable group that we have a hard time accessing, and I would really, really recommend urging that we get this for adolescents.

DR. LEVY: And I agree with Janet; that's a great point. And as a pediatrician, that 18 mark is, you know, kind of pulled out of a hat and, you know, has just kept -- promulgated with a lot of problems associated with it. I noticed that one of the studies presented by the Sponsor went down to age 11 years; did I see that correct?

DR. EDWARDS: There were a few --

DR. LEVY: Very few, yeah.

DR. EDWARDS: -- that were excluded. But Dr. Lynfield and I used our combined math ability during the dinner to just remind us that the routine use of vaccine for infants has been now 26 years, so there's a lot of people, obviously not 100%,

but a lot of children that had been immunized.

DR. ENGLUND: But are immigrants and the people who move here and -- so I still think that the adolescent -- I would also suggest it would be nice, maybe, to have --

DR. EDWARDS: Further studies, perhaps.

DR. ENGLUND: -- further studies in HIV positive, especially those who may not be as well controlled, because this vaccine looks so good that you could maybe use it even if they're not well controlled at the beginning, yeah. Excluded from this, from this study, right? Yeah.

DR. EDWARDS: So some of those special populations that were excluded might be included, and also some studies of the people who don't respond to the routine, or even a mix-and-match to see whether one dose would do the trick, perhaps.

Yes, Dr. Hoofnagle.

DR. HOOFNAGLE: Yeah, I agree with the non-responder, and this way you can bring in the adolescents who should've gotten a hepatitis B vaccine, and if they have substandard levels below 10, use of this vaccine to boost would be nice to show the safety and efficacy in that situation. And immunosuppressed patients, not just HIV, but people on corticosteroids, bone marrow transplant recipients, liver transplant recipients.

And then let me bring up the issue of what hepatologists are very involved with, which is reactivation of hepatitis B,

and what this is, is you've recovered from hepatitis B, but it comes back; it's a DNA virus and it persists for life. So you can be completely recovered and have antibody, and if you're immunosuppressed or have a bone marrow transplant, hepatitis B comes roaring back and can be quite severe. The mortality rate is 10%. So these people are usually given hepatitis B therapies to prevent reactivation.

But the Japanese have shown that if you have a titer of antibody above 100, which is reachable by these vaccines, the reactivation in that situation doesn't occur.

So this would be a wonderful situation, kind of, to test that as opposed to a lifelong use, like a bone marrow transplant patient, lifelong use of hepatitis B viral -- antiviral. So that's another niche area but an area that can give you fast and very important data. That's not so much safety as efficacy, but the safety comes in the immunosuppressed person, certainly in the transplant patients who have very high rates of coronary disease and stroke and so forth.

DR. EDWARDS: Thank you.

Any other additional study designs or --

DR. PORTNOY: Yeah, I would just like to -- the comment that the CpG adjuvant, the TLR9 agonist that we're talking about has been studied in allergen immunotherapy studies. I know that there were a number of studies done looking at that;

the abstracts weren't approved because efficacy was hard to demonstrate for a variety of reasons. But you could check with those studies and see what the safety data shows about cardiovascular events in those studies. It's something that you might want to take a look at.

DR. PACKER: Just a question. What was the age range in those studies?

DR. PORTNOY: It was -- well, I think they were adults. I don't know that they went up to, really, old adults whose -- it was allergic individuals, so most of the people in those studies would be in their 20s and 30s, but I know they included people in their 50s and 60s. I don't recall hearing, or at least I don't recall, any information about cardiovascular events in those studies. But it's something that you might want to take a look at.

DR. EDWARDS: Dr. Coffman.

DR. COFFMAN: Can we turn this on? Yeah, thank you. Bob Coffman, Dynavax.

I guess I'm the only survivor of the days when we had -- were working on that project. We didn't really include -- deal with that so much in the safety. I actually don't know whether we saw any cardiovascular events. Certainly, the overall safety profile was reasonably pristine on all those studies.

But I do want to point out, although the people got multiple injections, usually six, it was in a form of a

conjugate with an allergen, and the actual doses were much, much lower, most about 20 or 30 µg per injection rather than 3 mg. So I think it has limited value for our discussion, in any event. We'll go back and look. We didn't even actually dig up that data in terms of this filing.

DR. EDWARDS: Thank you.

DR. BENNINK: But Bob, in the -- you're doing a lot of cancer ones as well.

DR. COFFMAN: Yeah.

DR. BENNINK: I mean, are those higher doses or are those all relatively small numbers of people, too?

DR. COFFMAN: Still fairly small numbers of people, you know, in terms of other therapeutic programs with our cancer drugs, both cancer in a trial and hepatitis C patients. We're up to maybe 150 people there. We've not seen any signal, I don't recall a signal for MI, but I think the numbers are too small to include.

DR. EDWARDS: Okay. So, Dr. Gruber, are there any other questions that you would -- it looks like we have addressed them. Are there any other comments?

DR. GRUBER: Let me just confer with my colleagues.

DR. EDWARDS: Please.

(Pause.)

DR. GRUBER: We're good. We thank the Committee.

DR. EDWARDS: Okay. And I want to thank the Committee and

also the FDA and the Sponsors for the very succinct and clear presentations and for the new product.

CAPT HUNTER-THOMAS: Thank you, everyone. And this meeting is now adjourned.

(Whereupon, at 3:22 p.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

147TH MEETING OF THE VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

July 28, 2017

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Biologics Evaluation and Research.

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Dominico Quattrociocchi

Court Reporter