

UNITED STATES OF AMERICA  
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

|   |                                |
|---|--------------------------------|
| KATHRYN EDWARDS, M.D.                   | Chair                          |
| JANET ENGLUND, M.D.                     | Voting Member                  |
| 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.,<br>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                  |
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| MARIE R. GRIFFIN, M.D., M.P.H.          | Temporary Voting Member        |
| JAY H. HOOFNAGLE, M.D.                  | Temporary Voting Member        |
| 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.)

1  
2  
3 DR. EDWARDS: My name is Dr. Kathy Edwards. I'm from  
4 Vanderbilt University. I'm the VRBPAC Chair, and I'd like to  
5 welcome you all this morning, the members, the participants,  
6 the public, and the audience viewing on the webcast.

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

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

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

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

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

23 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20 DR. EDWARDS: Thank you very much.

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

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

1 would like to welcome you all today to this meeting.

2 Dr. Edwards is your Chair for this meeting.

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

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

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

11 COURT REPORTER: Close enough.

12 CAPT HUNTER-THOMAS: Close enough. Thank you.

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

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

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

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

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

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

4 The Food and Drug Administration is convening today, July  
5 28th, 2017, for the 147th meeting of the Vaccines and Related  
6 Biological Products Advisory Committee under the authority of  
7 the Federal Advisory Committee Act of 1972. This meeting is  
8 determined to be a particular matter involving specific  
9 parties.

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

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

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

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

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

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

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

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

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

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

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

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

25           This concludes my reading of the Conflict of Interest

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

3 Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

14 Engerix-B, for people from birth through 19 years of age,  
15 receive 10 µg of hepatitis B surface antigen three times at 0,  
16 1, and 6 months. For people 20 years of age and older, they  
17 receive 20 µg of surface antigen at 0, 1, and 6 months. And  
18 adults on hemodialysis receive 40 µg of surface antigen at 0,  
19 1, 2, and 6 months.

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



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

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

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

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

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

1 vaccines.

2       And the vaccine is indicated for immunization against  
3 infection caused by all known subtypes of hepatitis B virus in  
4 adults 18 years of age and older. And the dosage consists of  
5 two doses, 20 µg of hepatitis B surface antigen combined with  
6 3,000 µg of the CpG 1018 adjuvant, and this is given at a  
7 0- and 1-month schedule.

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

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

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

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

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

16 So I'd now like to talk a little bit about the use of  
17 anti-HBs antibody to predict protection. So early hepatitis B  
18 vaccine trials used the prevention of HBV infection as the  
19 clinical endpoint. The data from those early HBV vaccine  
20 studies, which actually used Heptavax, a plasma-derived  
21 hepatitis B surface antigen vaccine no longer on the market,  
22 showed antibody levels to the surface antigen of greater than  
23 10 mIU/mL, and this correlated with protection.

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

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

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

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

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

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

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

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

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

13 A VRBPAC meeting was held in November 2012 to discuss the  
14 immunogenicity and safety of the vaccine in adults 18 through  
15 70 years of age, and the committee members voted 13 to 1 that  
16 the immunogenicity data were adequate to support effectiveness.  
17 The committee members also voted 5 to 8 with 1 abstention that  
18 the available data were adequate to support safety. And it was  
19 noted that in view of the novel adjuvant, members recommended a  
20 larger pre-licensure safety database.

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

1 safety of Heplisav-B.

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

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

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

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

13 Thank you.

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

16 (No response.)

17 DR. EDWARDS: Thank you very much.

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

22 Dr. Janssen.

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

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

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

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

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

16 Heplisav is a sterile liquid dosage form. It comes in  
17 half mL dose vials, and it contains 20 µg of surface antigen  
18 and 3 mg of 1018. It's administered in a two-dose series  
19 1 month apart by intramuscular injection compared with the  
20 three-dose series over 6 months for the currently approved  
21 vaccines.

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

1 virus infection in adults.

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

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

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

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

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

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



1 14,000 adult participants. The focus of our presentation today  
2 will primarily be on data from our three pivotal trials.  
3 Individual data, key individual safety data from individual  
4 studies were presented in the briefing book.

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

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

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

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

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

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

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

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

5 DR. LEVY: Okay.

6 DR. EDWARDS: Thank you.

7 Dr. Schaffner, the Unmet Public Health Need.

8 DR. SCHAFFNER: Thank you, Dr. Edwards. Good morning.

9 I'm Bill Schaffner, Professor of Preventive Medicine and  
10 Infectious Diseases at the Vanderbilt University School of  
11 Medicine. I'm here today on World Hepatitis Day to discuss the  
12 public health need for an improved hepatitis B vaccine that  
13 overcomes the limitations of the currently licensed vaccines.

14 Hepatitis B transmission remains a problem with more than  
15 20,000 new infections each year and a 21% increase from 2014 to  
16 2015; 95% of these new infections occur in adults.

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

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

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

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

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

25       In the United States there are about 23 million adults

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

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

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

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

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

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

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

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

1 90%.

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

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

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

14 Additionally, we know that adherence to the third dose at  
15 6 months is essential for most adults to be fully protected,  
16 but this is challenging to complete. As seen in this Vaccine  
17 Safety Datalink study, a high proportion received at least two  
18 doses, but only 54% completed the required three-dose series.

19 In another study in adults at very high risk for HBV  
20 infection, such as MSM with sexually transmitted diseases, only  
21 43% completed the vaccine regimen, and some of those took up to  
22 5 years to complete.

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

1 unprotected and at risk.

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

9       So what would an improved hepatitis B vaccine in adults  
10 look like? To me, such a vaccine would induce high  
11 seroprotection in all adults, especially those nonresponsive to  
12 the current vaccines. An improved vaccine would require fewer  
13 doses given over a shorter time than the current  
14 3-dose/6-month regimen. And, of course, equally important is  
15 that any new vaccine maintain the safety profile of the current  
16 vaccines.

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

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

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

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

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

9 DR. EDWARDS: Other questions?

10 (No response.)

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

15 Stanley.

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

22 So in the next few slides, I will describe the adjuvants a  
23 little bit more extensively than Dr. Major has, which is called  
24 1018, and summarize our current understanding of its mechanism  
25 of action.



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

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

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

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

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

25           While Heplisav would be the first vaccine to specifically

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

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

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

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

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

1 hepatitis B surface antigen.

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

10       1018 is distinctive in that it targets a single well-  
11 characterized receptor and a specific subset of plasmacytoid  
12 dendritic cells. In fact, 1018 improves upon alum, not by  
13 being more potent or long lived but by being uniformly active  
14 in nearly all subjects and being much less compromised by age  
15 and health status.

16       Now, while the actions of 1018 are focused at the  
17 injection site and draining lymph node at the doses used in  
18 Heplisav-B, toxicology studies using repeated high doses of  
19 1018 allow us to evaluate the potential systemic effects of  
20 1018. 1018 was given weekly to monkeys at doses up to 270-fold  
21 greater than used in Heplisav and were generally well  
22 tolerated. The findings in major target organs of the monkeys,  
23 such as spleen and liver, were largely consistent with TLR9-  
24 mediated immune stimulation and were reversible after 4 weeks.  
25 More specifically, there were no effects on the cardiovascular

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

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

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

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

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

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

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

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

6 DR. LEVY: A question.

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

8 DR. LEVY: Yes.

9 DR. EDWARDS: Ofer.

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

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

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

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

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

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

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

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

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

21 DR. BENNINK: Yeah.

22 DR. EDWARDS: Dr. Bennick.

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

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

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

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

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

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

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

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

1 typical.

2 DR. PACKER: One more?

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

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

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

9 DR. COFFMAN: Yes. Bob Coffman.

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

19 DR. EDWARDS: Dr. Hoofnagle.

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

23 DR. COFFMAN: Bob Coffman.

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



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

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

9 DR. EDWARDS: Any other questions?

10 (No response.)

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

14 DR. JANSSEN: Thanks, Dr. Plotkin.

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

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

25 Seroprotection is defined as the level of antibodies

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

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

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

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

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

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

1 frequently used by clinicians in the United States.

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

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

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

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

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

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

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

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

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

19 The primary endpoint was met. The SPR in the Heplisav  
20 group was non-inferior to that in the Engerix group, and it was  
21 statistically significantly higher. The SPR in the Heplisav  
22 group at Week 12 was 95%; in the Engerix group at Week 28,  
23 81.2%. The difference between SPRs was 13.7%, with the lower  
24 bound of the 95% confidence interval of the difference in SPRs  
25 of 10.4%.

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

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

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

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

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

25           A key secondary endpoint was to demonstrate that the

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

3         Similar to HBV-10, HBV-16 met its primary endpoint,  
4 demonstrating that seroprotection with Heplisav is non-inferior  
5 to that of Engerix. In HBV-16, the SPR in the Heplisav group  
6 at Week 12 was 90.1%, and in the Engerix group at Week 32,  
7 70.5%. The difference between SPRs was 19.6%, with a lower  
8 bound of the 95% confidence interval of 14.7%. Additionally,  
9 Heplisav achieved its key secondary endpoint of a statistically  
10 significantly higher SPR.

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

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

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

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

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

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

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

25 Turning to the results of the secondary endpoints,

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

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

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

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



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

5 Now let's move to safety.

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

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

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

14 DR. EDWARDS: Janet.

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

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

1 DR. EDWARDS: Dr. Sawyer.

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

5 DR. JANSSEN: Primarily systemic steroids.

6 DR. EDWARDS: Dr. Levy.

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

10 DR. JANSSEN: We did not, no.

11 DR. EDWARDS: Dr. Hoofnagle.

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

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

15 DR. EDWARDS: Other immunogenicity questions?

16 (No response.)

17 DR. EDWARDS: Okay, then please proceed.

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

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

25 We'll present integrated safety data today for our three

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13 In the primary safety population, the most frequent new-  
14 onset immune-mediated event was Bell's palsy, occurring in  
15 0.06% of the Heplisav group, 0.05% in the Engerix group. The  
16 only other event that occurred in more than one Heplisav  
17 subject was hypothyroidism.

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

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

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

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



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

3 The event of Guillain-Barre syndrome occurred more than  
4 3½ months after the last Heplisav dose and 5 days after an  
5 influenza vaccination. The event of cavernous sinus syndrome  
6 is thought to be an inflammatory condition of Tolosa-Hunt  
7 syndrome but was not confirmed radiologically. This occurred  
8 8½ months after the last Heplisav injection.

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

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

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

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

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

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

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

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

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

15 In HBV-23, we conducted a lab sub-study of  
16 anti-phospholipid antibodies because of the numerical imbalance  
17 in pulmonary emboli in the previous BLA submission, in which  
18 0.11% of Heplisav subjects and no Engerix subjects had  
19 pulmonary embolus. Of note, pulmonary emboli were balanced  
20 between the treatment groups in HBV-23, 0.05% in the Heplisav  
21 group, 0.07% in the Engerix group.

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

1 relatively uncommon and were balanced between the groups.

2 The proportion of subjects who developed elevated anti-  
3 beta-2 glycoprotein 1 IgM levels was higher in the Heplisav  
4 group than in the Engerix group at Week 8. Importantly, there  
5 was no difference in any beta-2 glycoprotein 1 IgG. Isolated  
6 elevation of anti-beta-2 glycoprotein 1 IgM has not been  
7 associated with thrombotic disease in the literature, and in  
8 this study, no one with an elevated anti-beta-2 glycoprotein  
9 1 IgM had a thrombotic event.

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

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

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

25 In the primary safety population, the percentage of

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

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

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

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

1 HBV-23.

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

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

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

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

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

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

22 Okay, please.

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

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

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

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

11 DR. EDWARDS: Dr. Packer.

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

19 DR. JANSSEN: Dr. Coffman.

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

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

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

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

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

20 Dr. McGuire.

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 For cardiovascular event adjudication, all potential

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

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

7 Although the Heplisav trials were not dedicated  
8 cardiovascular trials, I found it remarkable that for 18 of the  
9 21 reported nonfatal MIs identified by the SMQ process, cardiac  
10 biomarker data were available. And for all but one of the  
11 reported acute myocardial infarction cases, cardiac  
12 catheterization data were also available. These data coupled  
13 with remarkably complete clinical annotations for all MI events  
14 allowed for meaningful adjudication of the potential acute  
15 myocardial infarctions. Let's look at the results.

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

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

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

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

19 Now, with the same format, the timing of occurrence of  
20 myocardial infarctions is plotted, again presented as incidence  
21 per thousand subjects. MIs were scattered over the duration of  
22 the trials with no evidence for clustering of events  
23 immediately following vaccine administrations. Almost one-  
24 third of the reported MIs in the Hcpilisav group, that is, 5 of  
25 16 events, occurred more than 300 days following the last

1 vaccine administration.

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

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

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

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

1           Finally, I considered a series of possible vaccine-induced  
2 causes of MIs or MACE outcomes, finding no evidence or support  
3 for any of them. There was no imbalance in events shortly  
4 after vaccine administration, as would have been expected if  
5 1018 mimicked an acute infection during the period of greatest  
6 reactogenicity.

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

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

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



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

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

13 Thank you.

14 Dr. Janssen.

15 DR. EDWARDS: Thank you.

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

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

25 DR. EDWARDS: Thank you.

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

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

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

1 actually, I'm not sure.

2 (Laughter.)

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

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

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

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

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

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

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

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

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

22 DR. PACKER: That would be great.

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

25 DR. PACKER: All right.

1 DR. McGUIRE: So these are the --

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

19 DR. JANSSEN: Dr. Coffman, please.

20 DR. COFFMAN: Bob Coffman, Dynavax.

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



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

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

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

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

1 think, in the first place.

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

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

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

1 well.

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

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

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

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

1 Study 16 and 10 and whether --

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

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

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

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

10 (Laughter.)

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

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

15 DR. PACKER: Oh.

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

17 DR. EDWARDS: Thank you.

18 Dr. Packer.

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

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

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

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

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

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

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

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

16 DR. McGUIRE: The short answer is there's no way to know.  
17 The reassurance is there's not an extreme imbalance in the  
18 background risk factors, as is shown here. It's perfectly  
19 balanced between the two groups in the 2:1 allocation sequence,  
20 100 versus 50, early on. But at the end of the day, one or two  
21 or three events would really materially change the ratios, and  
22 I fully understand that. So there's no way to know. They're  
23 still small numbers and it's still post hoc, but it's something  
24 that is lingering, which leads to the requirement for further  
25 evaluation in the postmarketing study you'll hear about.

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

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

8 DR. PACKER: Oh, okay.

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

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

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

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

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

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

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

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

6 DR. COFFMAN: Bob Coffman, Dynavax.

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

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



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

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

8           DR. COFFMAN: Right, right.

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

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

21           DR. EDWARDS: Dr. Ward.

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

1 DR. JANSSEN: Nothing, no.

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

5 DR. JANSSEN: No, postmarketing.

6 DR. EDWARDS: Postmarketing plan, yes. Sorry. Thank you.

7 DR. JANSSEN: Thank you, Dr. McGuire.

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

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

17 We're proposing to evaluate 40,000 vaccine recipients,  
18 20,000 of whom receive Hepilisav compared with 20,000 who  
19 receive another hepatitis B vaccine. Now, it's anticipated  
20 conservatively that the entire 40,000 patients will accrue  
21 within 1 year. Data will be collected through 13 months after  
22 the first dose of vaccine.

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

1 anaphylaxis.

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

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

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

14 The proposed sample size of the postmarketing study has  
15 87% power to detect an increased risk greater than or equal to  
16 2.5 for an event assuming a background incidence of 1 per 1,000  
17 for an immune-mediated event.

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

25 The overall serious adverse event rate was similar for the

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

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

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

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

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

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

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

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

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

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

18 Yes, Mark.

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

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

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

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

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

15 DR. JANSSEN: Yes. Yeah. Yeah, and they vaccinate people  
16 18 to 79, actually, based on their data from the last several  
17 years.

18 DR. EDWARDS: Dr. Kotloff.

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

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

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

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

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

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

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

14 DR. JANSSEN: Yeah. Could we have the CRP slide? We did  
15 CRP in HBV-10, and what we saw was -- it's a little  
16 complicated. If you look at baseline, if you look at the  
17 normal at baseline and then look at high for Visit 5, which is  
18 4 weeks and Visit 7 is 8 weeks -- it's 12 weeks, actually, and  
19 this is -- as you can see in the Heplisav group, at Visit 5 it  
20 was 7% had high CRPs compared to 10% in the Engerix group, and  
21 then at 12 weeks it was 9 compared to basically 9. So we  
22 didn't see any evidence of a difference in CRP.

23 DR. EDWARDS: Dr. Packer.

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

1 what a normal CRP is, from a cardiovascular risk point of view.

2 Also, was that a high sensitivity assay or --

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

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

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

10 DR. PACKER: Sure.

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

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

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

25 Oh, Darren?



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

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

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

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

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

4           DR. EDWARDS: Jack.

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

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

20           DR. MCGUIRE: Darren McGuire, UT Southwestern.

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

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

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

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

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

1 adults in the U.S.

2 By way of experience, I've been a practicing internist for  
3 36 years. I've been the PI of roughly 40 vaccine clinical  
4 trials, involved in many more, and exposed to hundreds more as  
5 the Editor-in-Chief of the journal *Vaccine*. I was the chair of  
6 the safety evaluation and adjudication committee, or SEAC, for  
7 the HBV-16 and 23 trials. Unfortunately, I've also seen more  
8 cases of hepatitis B and its sequelae than I would have ever  
9 wanted to see in my career.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

17 Thank you.

18 DR. EDWARDS: Are there any other pressing questions?

19 (No response.)

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

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

1 immunogenicity evaluation of Heparisav-B along with updates  
2 regarding this analysis.

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

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

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

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

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

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

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

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

15 Success criteria for these studies were defined as a non-  
16 inferiority margin of 10% for the between group difference in  
17 SPRs. Non-inferiority was established if the lower two-sided  
18 95% confidence interval limit around the Heplisav-B SPR minus  
19 the Engerix-B SPR was greater than -10%.

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

25 I need to mention that Study 10 also randomized and

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

4 Study HBV-16 enrolled adults 40 to 70 years of age. They  
5 were randomized 4:1 to Heplisav-B or Engerix-B. A total of  
6 2,452 subjects were enrolled, with 1,969 subjects enrolled to  
7 the Heplisav-B arm and 483 subjects enrolled to the Engerix-B  
8 arm.

9 I will now summarize the immunogenicity results for  
10 Studies 10 and 16. Before I discuss the actual findings, I  
11 want to reiterate that the clinical study reports for Studies  
12 10 and 16 were revised in 2016 to reflect revised subject  
13 accounting for the per-protocol populations for both of these  
14 studies. The change in the per-protocol population numbers  
15 were negligible.

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

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

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

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

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

16           DR. EDWARDS: Questions?

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

23           Okay, break now? Raise your hand.

24           (Show of hands.)

25           DR. EDWARDS: Okay, no break.

1 (Off microphone comment.)

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

3 (Laughter.)

4 DR. EDWARDS: Let's do it again.

5 Break now?

6 (Show of hands.)

7 DR. EDWARDS: No break. Okay.

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

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

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

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

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

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

7 The proposed indication is for immunization against  
8 infection caused by all known subtypes of hepatitis B in adults  
9 18 years of age and older. Heplisav-B is administered as a  
10 two-dose series of 0.5 mL administered 4 weeks apart.

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

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

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

25 The FDA integrated analysis of safety will primarily focus

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

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

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

15 Serious adverse events were collected for 28 weeks in  
16 Study 10, for 52 weeks in Study 16, and for 56 weeks in Study  
17 23.

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 both treatment groups.

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

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

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

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

25       In order to identify all events of myocardial infarction,

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

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

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

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

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

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

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

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

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

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

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

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

18           Based on the selected preferred terms, 11 deaths in the  
19 Hheplisav-B group and 3 deaths in the Engerix-B group were  
20 selected by Dynavax consultants for blinded adjudication.  
21 Three deaths in the Hheplisav-B group and one death in the  
22 Engerix-B group were adjudicated as cardiovascular deaths. One  
23 death in the Hheplisav-B group and two deaths in the Engerix-B  
24 group were adjudicated as not a cardiovascular death.

25           There were seven subjects in the Hheplisav-B group and no

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

25 Point three percent of subjects in the Heplisav-B group

1 reported events that the SEAC adjudicated as autoimmune and  
2 0.4% of subjects in the Engerix-B group reported events that  
3 they adjudicated as autoimmune. And of these events, four  
4 subjects in the Hekplisav-B group and zero subjects in the  
5 Engerix-B group reported events that the SEAC adjudicated as  
6 new-onset autoimmune events. And the SEAC did not adjudicate  
7 any events as related.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 determination of whether or not it was a cardiovascular event.

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

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

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

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

15 SAEs were collected in all three pivotal studies but were  
16 monitored for 28 weeks in Study 10, 52 weeks in Study 16, and  
17 56 weeks in Study 23.

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

1           The integrated summary of safety included three different  
2 safety populations for evaluation of SAEs. The primary safety  
3 populations, or PSPs, included a 6-month PSP and a 1-year PSP.  
4 The 6-month PSP included Studies 10, 16, and 23 and evaluated  
5 SAEs reported within the first 6 months following dose 1. The  
6 1-year PSP included Studies 16 and 23 and evaluated SAEs that  
7 were reported for 1 year following dose 1. Study 10 was  
8 excluded from this analysis as SAEs were only collected for  
9 6 months.

10           And the modified total safety population, or mTSP,  
11 included Pivotal Studies 10, 16, and 23 and Supportive Studies  
12 14 and 22 and evaluated SAEs reported within the first 6 months  
13 following dose 1.

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

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

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

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

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

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

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

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



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

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

9 Overall, serious adverse events were reported at similar  
10 rates between treatment groups in both the 6-month and the  
11 1-year primary safety population. There were 34 deaths  
12 reported in the Heplisav-B clinical development program. All  
13 were discussed previously in this presentation: 32 reported in  
14 Study 23 and 2 reported in Study 16.

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

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

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

7           The preferred terms are listed on the left with columns  
8 for each treatment group in Studies 23, 16, and 10 as you move  
9 from left to right. As we saw before, there were 19 subjects  
10 in the Heplisav-B group and 3 subjects in the Engerix-B group  
11 who reported myocardial infarction in Study 23. In Study 16,  
12 three subjects were identified with myocardial infarctions by  
13 preferred term search, two in the Heplisav-B group, and one in  
14 the Engerix-B group. The subject in the Engerix-B group had  
15 two adverse events with two preferred terms that represented  
16 the same event. And please keep in mind that this study had a  
17 4:1 randomization ratio. And there were no events of  
18 myocardial infarction that were identified in Study 10.

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

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

10           When reviewing the number of events per group, please note  
11 that Study 23 had a 2:1 randomization ratio and Study 16 had a  
12 4:1 randomization ratio.

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

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

1 subjects that had an event that was adjudicated as stroke.

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

10 However, please keep in mind that the findings were  
11 observed in a randomized controlled trial where the most valid  
12 comparison is to the Engerix-B group within the study and that  
13 the relative risk of myocardial infarction in Study 23 was  
14 6.97.

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

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

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

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

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

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

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

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

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

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

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

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

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

19 The randomization ratio for these two studies was  
20 approximately 3.5, so 0.2% of Heplisav-B recipients and 0.1% of  
21 Engerix-B recipients reported herpes zoster. And this is  
22 compared to the 0.7% Heplisav-B recipients and 0.3% Engerix-B  
23 recipients who reported the event in Study 23. And in Study  
24 23, medically attended adverse events were monitored for twice  
25 as long as adverse events in Studies 10 and 16.

1           So moving on to AESIs, AESIs were collected prospectively  
2 in Pivotal Studies 16 and 23, and they both utilized SEAC  
3 adjudication. So I'll present an integrated analysis of these  
4 two studies here followed by analysis of studies that did not  
5 prospectively collect AESIs. So in Study 23 and 16, new-onset  
6 AESIs were identified in 15 subjects in the Hcpilisav-B group or  
7 0.2%, and one subject in the Engerix-B or 0.3%.

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

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

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



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

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

11       So Dynavax searched the safety database of these trials  
12 for preferred terms from the list of AESIs that was used in the  
13 studies that prospectively collected AESIs. So I'd like to  
14 note that this evaluation includes studies that did not use the  
15 final formulation dose or schedule. In these studies, new-  
16 onset AESIs were identified in six subjects in the Heplisav-B  
17 group, or 0.2%, and in five subjects in the Engerix-B group, or  
18 0.5%.

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

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

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

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

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

1 was possibly related to study treatment.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7       Because of this imbalance, a major adverse cardiovascular  
8 events analysis, which included blinded adjudication of events  
9 of cardiovascular death, MI, and stroke in the three pivotal  
10 trials, was conducted. The MACE analysis showed that in Study  
11 23 there were 14 subjects in the Heplisav-B group and 1 subject  
12 in the Engerix-B group who had an SAE adjudicated as MI. And  
13 differences between treatment groups in events of adjudicated  
14 cardiovascular death, although few, and adjudicated stroke  
15 trended in the same direction.

16       An imbalance in myocardial infarction in the composite  
17 three-point MACE outcome was not observed in other trials.  
18 However, Studies 16 and 10 enrolled populations with lower  
19 prevalences of known risk factors for cardiovascular disease.  
20 The difference in risk between treatment groups was noted  
21 approximately 3 months after first vaccination, which is  
22 2 months after second vaccination, and persisted through the  
23 study follow-up period. Subjects who reported myocardial  
24 infarctions all had risk factors for cardiovascular disease.  
25 Reported risk factors were similar between treatment groups at

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

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

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

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

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

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

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

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

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

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



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

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

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

18 The analysis will also be performed for each event of  
19 interest separately. For these analyses, the power would be  
20 limited since, for example, the background incidence rate for  
21 granulomatosis with polyangiitis is approximately 0.8 to 1 per  
22 100,000 person-years and the background incidence for  
23 Tolosa-Hunt syndrome has been assessed as approximately 1 to 2  
24 per 1 million person-years.

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

1 a hazard ratio of 2 or higher for herpes zoster after 2 years  
2 after the study starts assuming a background incidence rate of  
3 4 per 1,000 person-years.

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

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

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

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

15 Thank you.

16 DR. EDWARDS: Thank you.

17 Are there questions for Dr. Everett?

18 Yes, Ofer.

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

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

3 DR. PEREZ-VILAR: Silvia Perez-Vilar.

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

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

14 DR. PEREZ-VILAR: Yes.

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

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

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

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

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

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

7 DR. PEREZ-VILAR: Yes.

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

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

15 DR. EDWARDS: Dr. Monto.

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

19 DR. GRUBER: So this is Marion Gruber.

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

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

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

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

7 DR. EDWARDS: Yes, Karen.

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

14 DR. EDWARDS: FDA is going to comment.

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

24 DR. EDWARDS: Dr. Packer.

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

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

3 (Off microphone comment.)

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

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

17 DR. PACKER: Yeah.

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

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

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

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

4 DR. EDWARDS: Dr. Monto.

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

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

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

16 DR. EDWARDS: Dr. Griffin.

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

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

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

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

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

9 DR. EDWARDS: Good point.

10 Other comments?

11 Yes, Dr. Janssen.

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

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

17 DR. JANSSEN: No, I don't.

18 DR. PACKER: Okay, thank you.

19 (Off microphone comment.)

20 DR. PACKER: I get it, yeah.

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



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

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

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

19 In this case, for a confidence interval, conservative  
20 means that the interval is too wide. So we calculated Koopman  
21 score intervals as an alternative based both on the literature  
22 and on some simulations we performed. In this particular  
23 setting, these intervals have much closer to the coverage that  
24 they're supposed to have, that is a 95% interval really is a  
25 95% interval. The Wald interval is a 95% interval, and it

1 might be closer to a 98% interval here.

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

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

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

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

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

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

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

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

6 So these are the data that we're talking about. You've  
7 seen versions of this table several times today. When we're  
8 talking about a no-borrowing scenario, that's based only on the  
9 14 to 1 events of AMI in study HBV-23, and the full borrowing  
10 scenario is based on that same 14 to 1 plus the 2 to 1 in study  
11 HBV-16 along with the total denominator from all three studies.

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

15 So these are the results from the full borrowing scenario.  
16 This is the posterior distribution of relative risk. What this  
17 shows is that based on all three studies together, the  
18 posterior probability that the relative risk is greater than 1  
19 is 94.7%, the posterior probability that it's greater than 2 is  
20 65.5%, the posterior probability that it's greater than 3 is  
21 40.8%, and the posterior probability that the relative risk is  
22 greater than 5 is 17.3%. So that's the full borrowing  
23 scenario.

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

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

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

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

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

18 Thank you.

19 DR. EDWARDS: Thank you very much.

20 Are there questions? Comments?

21 Dr. Lee.

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

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

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

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

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

17 DR. LEE: Thank you.

18 DR. EDWARDS: Dr. Sawyer.

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

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

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

3 DR. EDWARDS: Dr. Packer.

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

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

14 DR. EDWARDS: Any other questions?

15 DR. KOTLOFF: I have one question.

16 DR. EDWARDS: Karen.

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

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

22 DR. EDWARDS: Questions?

23 (No response.)

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

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

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

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

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A F T E R N O O N   S E S S I O N

(1:30 p.m.)

1  
2  
3       DR. EDWARDS: Seated, and we'll begin the Open Public  
4 Hearing of the registered speakers.

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

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

12       DR. EDWARDS: Please.

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

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

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

1 work more as a control.

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

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

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

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

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

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

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

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

24 DR. EDWARDS: Thank you very much.

25 The next speaker will be Judy Weisman.

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

7 Interestingly, most of the transmission of the hepatitis  
8 among my patients is because of heterosexual sexual activity.  
9 When I ask about have they shared needles, they look horrified,  
10 "I would never do that," and you can buy needles over the  
11 counter in Maine. When I've asked them, well, how about would  
12 you be interested in a vaccine that requires two doses over a  
13 1-month period rather than three doses over a 6-month period,  
14 they look at me as if I have three heads. "Well, doc, you  
15 know, I don't like coming in here. Of course, I'd do it in two  
16 doses rather than three."

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

23 DR. EDWARDS: Thank you so much.

24 The next speaker will be Megan Polanin.

25 DR. POLANIN: Thank you for the opportunity to speak

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

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

12 We commend the FDA for closely analyzing the safety data  
13 and agree that the affect on adverse events is unclear. We  
14 support the FDA's diligence in working with the company to  
15 develop future studies needed to address these safety concerns.

16 We commend the company for including more black patients  
17 in HBV-16 and HBV-23 as this group has a relatively high  
18 incidence of acute hepatitis B infection. However, Asians  
19 living in the United States account for more than half of the  
20 1 million Americans living with chronic hepatitis B. Chronic  
21 infection is responsible for most HBV-related morbidity and  
22 mortality. Clearly, Asians are not adequately represented in  
23 the company's pivotal trials. There's no way to know if the  
24 impact of the vaccine would be different for any Asian groups  
25 because too few Asians are included in the study.

1           In addition, the clinical trials took place in different  
2 countries with varying numbers of patients with diabetes, high  
3 BMI, or a history of smoking. These factors could also affect  
4 the risk-benefit ratio.

5           We feel for the company because it has previously tried  
6 and failed to obtain approval; however, the bottom line is we  
7 don't know how safe the vaccine is overall and specifically how  
8 safe it is for Asians who comprise the majority of patients  
9 living with chronic hepatitis B.

10           It is better for FDA to be cautious rather than approve a  
11 potentially dangerous vaccine, especially because other options  
12 are available. We strongly urge this Advisory Committee to  
13 prioritize patient safety and urge the FDA to maintain its  
14 scientific safety standards for approval and therefore  
15 recommend additional pre-licensure studies to further evaluate  
16 the safety of Heplisav-B in subpopulations who are  
17 disproportionately affected by both acute and chronic hepatitis  
18 B infection.

19           DR. EDWARDS: Thank you very much.

20           Dr. David Thomas.

21           DR. THOMAS: I have no conflicts of interest to disclose,  
22 and I'm going to read my comments in the interest of time.

23           As a physician caring for adults with infectious diseases  
24 and an epidemiologist aware of the public health impact of  
25 viral hepatitis, I strongly support HBV vaccine development.

1           Hepatitis B is a major public health problem that's  
2 preventable, and yet many adults remain at risk of infection.  
3 For example, in the most recent representative sample of the  
4 U.S. general population, vaccine-induced protection against  
5 hepatitis B was noted in just 29% of adults 20 to 50 years of  
6 age and just 9% of those more than 50.

7           HBV infections continue to occur among adults, and the  
8 incidence has actually risen in association with the national  
9 opioid outbreak. New infections also continue to occur among  
10 persons with diabetes, high-risk same-sex and heterosexual  
11 exposures, and among persons who inject drugs. And we are  
12 seeing a resurgence of relapsing infections brought on by the  
13 expanding use of immunosuppressive agents.

14           Unfortunately, the immunogenicity and completion rates of  
15 the current HBV vaccines are lower in many of the same  
16 populations who most need protection, including persons with  
17 diabetes, those on dialysis, and HIV-infected persons compared  
18 to healthy adults or children. For example, in most real-world  
19 settings, only 55 to 60% of persons complete their vaccine  
20 series, and even among those who do, 10 to 40% may fail to  
21 achieve protective immunity.

22           Therefore, from a clinical and epidemiologic perspective,  
23 we enthusiastically support development of more immunogenetic  
24 and simpler vaccine products for our adult patients.

25           DR. EDWARDS: Thank you very much.

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1 The next speaker will be Ryan Clary.

2 MR. CLARY: Good afternoon. I have no financial  
3 relationship with Dynavax.

4 My name is Ryan Clary, and I'm the Executive Director of  
5 the National Viral Hepatitis Roundtable. We are a coalition of  
6 over 500 organizations around the country working to fight and  
7 ultimately end the hepatitis B and C epidemics in the United  
8 States. As you review this application, I ask that you  
9 consider the following points:

10 First and foremost, hepatitis B disproportionately affects  
11 Asian American and Pacific Islanders. Hepatitis B affects 1 in  
12 12 AAPIs, and while Asian Americans and Pacific Islanders make  
13 up 5% of the U.S. population, they account for more than 50% of  
14 the hepatitis B cases in the country. These are unacceptable  
15 statistics that require a sense of urgency in providing new  
16 effective prevention tools in order to address a serious health  
17 inequity.

18 In March 2017, the National Academies of Sciences,  
19 Engineering, and Medicine released a national strategy for the  
20 elimination of hepatitis B and C, stating emphatically that the  
21 public health impact of hepatitis B and C could be eliminated  
22 by the year 2030 and outlining specific recommendations to lead  
23 the nation towards this goal.

24 One of the recommendations calls for expanded access to  
25 adult hepatitis B vaccination, noting that as of 2014, only a



1 quarter of adults over the age of 19 were fully immunized. The  
2 public health benefit of a two-dose over 1-month hepatitis B  
3 vaccine would move the United States forward in achieving  
4 elimination goals.

5 In May 2017, the CDC released disturbing statistics  
6 showing a 20% increase in acute hepatitis B infections in 2015.  
7 The increase is largely the result of injection drug use tied  
8 to the nation's opioid crisis. An effective vaccine with fewer  
9 doses taken over a shorter period of time could be provided to  
10 at-risk adults at syringe access programs, substance abuse  
11 treatment services, and other appropriate settings to protect  
12 them from a serious and sometimes fatal disease and to slow or  
13 stop new infections.

14 Finally, I would like to share a personal story that led  
15 me to this work. In March 2001 my partner was rushed to the  
16 emergency room with internal bleeding. Five days later he  
17 learned he had chronic hepatitis B and inoperable liver cancer.  
18 He was given 6 months to live and lived 5 months, dying at the  
19 age of 33.

20 It's impossible to know what might have saved his life,  
21 but every day I hope for advancements in hepatitis B and liver  
22 cancer prevention care and treatment so no one else has to  
23 endure a similar tragic loss. A new hepatitis B vaccine that  
24 improves the chance an individual will complete the series will  
25 make it more likely that my hope is fulfilled.

1           In summary, NVHR respectfully urges you to consider this  
2 public health and personal perspective.

3           Thank you.

4           DR. EDWARDS: Thank you very much.

5           Joan Block.

6           MS. BLOCK: Thank you. I'm with the Hepatitis B  
7 Foundation, which we established in 1991. It's the only  
8 national nonprofit research and disease advocacy organization  
9 for hepatitis B. And I just want to let you all know, today is  
10 World Hepatitis Day. The WHO designated July 28th as this day  
11 because it's the birth date of Dr. Baruch Blumberg, who won the  
12 Nobel Prize for his discovery of the hepatitis B virus.  
13 Dr. Blumberg also invented the first hepatitis B vaccine, which  
14 the FDA itself designated the first anti-cancer vaccine.

15           As you know, the CDC has said that hepatitis B is the  
16 deadliest vaccine-preventable disease, and yet, 50 years later,  
17 hepatitis B is still killing almost 1 million people each year.

18           As a nurse, I have cared for patients dying with liver  
19 cancer due to hepatitis B. As co-founder of the Hepatitis B  
20 Foundation, I have literally spoken with thousands of patients  
21 and families who are living with the burden of hepatitis B. We  
22 talk a lot about prevention. The Hepatitis B Foundation is  
23 focused on those people who live with the disease every day and  
24 lose loved ones every day.

25           I'm here to urge the FDA Advisory Committee to consider a

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1 2-dose vaccine. The community-based screening programs that  
2 we've been doing in greater Philadelphia for the past 10 years  
3 has shown us that -- we did a special study 2011 to 2013 funded  
4 by the CDC to look at vaccination rates among adults in  
5 high-risk communities. We found that only 13% of adults  
6 completed the third dose, but 81% completed the second dose.  
7 Our finding is not unique; that is something that is found  
8 among the 30 other coalitions that we work with across the  
9 country conducting community-based screening and vaccination.

10 We know that if there is a two-dose vaccine, we would be  
11 able to save more lives every day, and we really truly could  
12 make hepatitis B history.

13 So thank you.

14 DR. EDWARDS: Dr. Kim, Ray Kim.

15 MS. BLOCK: I don't have any financial conflicts.

16 DR. KIM: Good afternoon. My name is Ray Kim. I'm an  
17 adult hepatologist working at Stanford University, and this is  
18 my opinion. I'm partially subsidized for this travel today.

19 As an Asian-American physician practicing in south San  
20 Francisco Bay area, I deal with hepatitis B patients every day  
21 that struggle with their infection lifelong. And it is  
22 important for us to have the right tools to fight the disease  
23 burden that is prevalent in Asian population.

24 I have two points to make: One, as was previously spoken,  
25 the adherence for the third dose is very, very, very difficult,

1 and it is even more difficult when we go out in the community  
2 to try to raise awareness and initiate a vaccination program.  
3 So having two-dose vaccines will be very important.

4 In terms of the study, I'd like to point out that the  
5 comparison between the two-dose and three-dose studies, if you  
6 take that to the real life, the discrepancy between the two  
7 study results will be even larger because most of the patients  
8 will not get the third dose. So take that into consideration  
9 in comparing the efficacy or effectiveness of the vaccine.

10 The second point that I'd like to make is the prevalence  
11 of chronic illness in our population, as was pointed out, there  
12 is a lot of patients who need this vaccine later in life with  
13 health risks, and those are the very patients in whom the  
14 response rate is low. We need a better tool to cover those  
15 patients.

16 And there was a question earlier today about whether we  
17 will be -- practicing physicians will be avoiding using  
18 Hепlisav in patients who have perceived risk, higher risk of  
19 having problems. I would argue that will be opposite since the  
20 response rate in the current regimen is so low that if this  
21 vaccine were to be available to us, we will go to that vaccine  
22 for those patients who are expected to have a low response  
23 rate.

24 Thank you.

25 DR. EDWARDS: Thank you very much.

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1 Dr. Kathleen Schwarz.

2 DR. SCHWARZ: Thank you. I am a pediatric hepatologist at  
3 Johns Hopkins with a particular interest in viral hepatitis.  
4 I'm in the hepatitis B research network of NIDDK, and I just  
5 retired from being the president of the International  
6 Organization of Pediatric Gastroenterologists, where we care  
7 for thousands of children with hepatitis B. My travel was  
8 supported by Dynavax, but I would've come if not.

9 So I'd like to emphasize the crying need for having a safe  
10 and effective easily administered vaccine particularly for  
11 young adults, and this is from my perspective of being in the  
12 trenches. I'm a liver transplant doctor, and what's happened  
13 with liver transplantation now in America is that one out of  
14 four cadaveric livers is a so-called high-risk donor. So these  
15 donors have a fairly high prevalence of anti-core antibody and,  
16 of course, have a risk of giving hepatitis B to the recipient,  
17 but since we have such long waiting lists, we're forced to use  
18 them.

19 My second perspective is from a grant I had to try to  
20 improve hepatitis B vaccination of homeless adolescents in  
21 Baltimore. I was motivated to apply for this grant from NIAID  
22 because we had a 15-year-old, years ago, inner-city Baltimore  
23 girl, who presented with fulminant hepatitis B; we had to do a  
24 liver transplant on Christmas Eve, and she died several years  
25 later of immunosuppression side effects.

1           So I said this is America, this is a vaccine-preventable  
2 disease, this should not be happening, so our grant addressed  
3 homeless adolescents. Four percent of them had a vaccine card  
4 saying that they'd had hepatitis B vaccine, and with heroic  
5 efforts, we did get most of them to accept the baseline vaccine  
6 and the 1-month vaccine, but very few to accept the 3-month  
7 vaccine.

8           And then the third is the global perspective from working  
9 around the world with pediatric gastroenterologists. We have  
10 decided to commit to global hepatitis B vaccine and in part our  
11 own experiences, and then the other is the very sobering  
12 statistic from Ott et al. that in 2005, a long period after  
13 introduction of the hepatitis B vaccine, the number of people  
14 around the world with hepatitis B actually grows. So 240  
15 million in 2005 versus 225 million in 1990.

16           Thank you.

17           DR. EDWARDS: Thank you very much.

18           The next speaker will be Dr. Vivian Huang.

19           DR. HUANG: Hi, I'm Dr. Vivian Huang. I'm from New York  
20 City. I work at the New York City Health Department. I am not  
21 representing the health department.

22           But I can tell you that New York City is at the epicenter  
23 of the hepatitis B silent epidemic. I can tell you that we  
24 have 8.6 million people in New York City, and of those, 3.1  
25 million are immigrants and top countries of people immigrating

1 from Dominican Republic, China, and Mexico. In New York City  
2 we have about approximately greater than 100,000 cases of  
3 chronic hepatitis B, which is more than those infected with  
4 HIV.

5 And I can also tell you that of concern since 2013, we've  
6 seen an increase in newly reported cases of hepatitis B in New  
7 York City. This is very concerning to me, and I don't know why  
8 this is happening.

9 I can also tell you that of the areas where we see high  
10 rates of hepatitis B, we are also seeing very low vaccination  
11 rates, so those places in Queens and also in Brooklyn, we're  
12 seeing about 30% vaccination rate. So clearly, we are failing  
13 to vaccinate our New Yorkers and protecting them against  
14 hepatitis B.

15 I can also tell you from the immunization clinic in New  
16 York City that we vaccinate over 6,000 -- we've given over  
17 6,000 vaccinations, and of those that have completed is 1,500,  
18 so that's 20%, which is another failure.

19 Another hat that I used to wear, I used to be the  
20 hepatitis B director at the Charles B. Wang Community Health  
21 Center, and one in eight of our patients have chronic hep-B,  
22 20% of our patients that are pregnant have hep-B, and also one-  
23 third of those that we screen are susceptible to hep-B.

24 The population that we see at our clinic is transient and  
25 migrant, and their inability to come back to get their 6-month

1 hep-B vaccine. They usually can come for their baseline and  
2 also their first month.

3 So I'm urging all of you here to recognize that New York  
4 City is a place of immigrants -- 40% are either foreign-born or  
5 children of foreign-born -- and we really need a vaccine that  
6 can take care of our patients, so I urge you to consider this  
7 vaccine.

8 Thank you.

9 DR. EDWARDS: Thank you.

10 Jane Pan.

11 MS. PAN: Good afternoon. My name is Jane Pan, and I'm  
12 with the Hepatitis B Initiative of Washington, D.C. I have no  
13 financial tie with Dynavax.

14 For over 10 years, our grassroots organization is a  
15 nonprofit organization and has been providing free hepatitis B  
16 education, screening, vaccination, and linkage to care services  
17 to at-risk adult communities in the D.C. metro area.

18 Over the past 10 years, we have provided in-person  
19 education to over 18,600 individuals, screened over 11,800. On  
20 average, 5% of the population we screen tested positive for  
21 hepatitis B and we are linked to -- positive to care. And 37%  
22 are vulnerable and needed hepatitis B vaccination.

23 While we have been successful in educating and screening  
24 community members, however, when it comes to vaccination, we  
25 have continued to see obstacles. Even when we are able to link



1 our patients to the first vaccine dosage, it has been difficult  
2 to get patients to come back within the 6-month time frame to  
3 complete the three vaccine dosages. From our experience and  
4 observation on our patients' behavior, we feel that two  
5 vaccines over a month regimen may be much easier for adults and  
6 could improve their adherence.

7 Out of the 4,331 patients, about -- that's about 37% of  
8 the populations that we have tested over the course of 10 years  
9 has needed vaccination. Only 20% have completed three dosages  
10 compared to 81% who have completed two dosages.

11 In closing, we would like the FDA Advisory Committee to  
12 consider the risk vulnerable community that includes working  
13 immigrants who have difficulties taking time off work to take  
14 care of their health. As healthcare providers, you want to  
15 seize the moment when we have them in your office or at your  
16 site to provide them with services that will also protect the  
17 general public's health of a deadly infectious disease such as  
18 hepatitis B. We hope that we're providing the valuable  
19 information for the Committee to consider.

20 Thank you very much for your time.

21 DR. EDWARDS: Thank you.

22 Nick Walsh.

23 DR. WALSH: Hi, my name is Dr. Nick Walsh. I'm the  
24 Regional Advisor for Viral Hepatitis at the Pan American Health  
25 Organization based here in D.C., which is also the regional

1 office for the Americas for the World Health Organization. My  
2 comments relate to the public health implications of the  
3 vaccine and the fact that the FDA is a stringent regulatory  
4 authority which has influence indirect and direct in other  
5 countries around the world. I have no conflicts.

6 In 2016 the countries of the world, the World Health  
7 Assembly, agreed to eliminate viral hepatitis as a public  
8 health threat by 2030. This is in line with the Sustainable  
9 Development Goals agreed some months before that.

10 In order to eliminate viral hepatitis as a public health  
11 threat, we need all tools at our disposal, both those for  
12 prevention vaccine and treatment, of course. We have no cure  
13 for hepatitis B. We have effective vaccines, and one is  
14 considered today.

15 Just relating to my brief, which is -- in the Americas,  
16 there's 2.8 million people living with hepatitis B. These are  
17 people with the infection and potentially could transmit to  
18 others. We have 90,000 new infections every year, which is 250  
19 new infections of hepatitis B every day.

20 We've been successful in immunizing infants, but a big,  
21 big gap is poor coverage among adults in the region. We don't  
22 have high hepatitis B vaccine coverage among unvaccinated --  
23 among adults at risk of infection. We believe that a shortened  
24 duration with less injections to fulfill the vaccine schedule  
25 can result in improved coverage.

1           This is critical right now because we're at the stage  
2 where we need to look at the margins, we need to identify the  
3 risk groups and increase vaccination rates among these  
4 particular risk groups right through the -- right around the  
5 region to prevent ongoing transmission if we are to achieve the  
6 regional goal, the global goal of the elimination of hepatitis  
7 as a public health threat.

8           Every infection prevented is another one, is another  
9 potentially -- another life saved. Each of these people is  
10 connected to a family. This is a preventable tragedy,  
11 hepatitis B, and I'll finish my comments, then.

12           Thanks.

13           DR. EDWARDS: Thank you very much.

14           Captain James Woody.

15           DR. WOODY: Good afternoon, I'm Dr. James Woody. I'm a  
16 pediatrician and a physician and a scientist. I retired as a  
17 U.S. Navy medical officer after 20 years, but I don't speak for  
18 the DoD.

19           By way of background, I have an interest in infectious  
20 diseases. My Navy colleagues and I started the National Marrow  
21 Donor Program, which you're probably all familiar with. I  
22 subsequently developed a drug called infliximab or Remicade,  
23 and I serve on the board of the Stanford Children's Hospital-  
24 Lucile Packard.

25           I retired as a captain in the medical corps of the U.S.

1 Navy. I was a commanding officer of the Navy Medical Research  
2 and Development Command. We had Navy research labs around the  
3 world. I had previously served as the commanding officer of  
4 NAMRU-3 in Cairo, Egypt for 4 years. So we conducted surveys  
5 for HIV, hepatitis, Ebola, Congo-Crimean -- and other pathogens  
6 worldwide. We saw hepatitis B in over 50% of the populations  
7 in all of these places like Sudan and Somalia and Yemen, which  
8 you've heard of, but I've been there. Same is true of  
9 Afghanistan, Syria, and Iraq.

10 My command was also tasked with infectious disease  
11 surveillance and bio-warfare for the first Gulf War. You may  
12 recall, we deployed 500,000 people suddenly over to the Gulf,  
13 many of them unimmunized.

14 So my comment is that the DoD policy of immunizing people  
15 is actually very good if you happen to have time. If you  
16 don't, it's not going to work. Immunizing people with a third  
17 dose at 6 months on a ship with 3- or 4,000 people as you're  
18 transporting them is a logistics nightmare; it just won't  
19 happen.

20 So my comment, if you have a combination of vaccine that  
21 gets good surveillance and good seropositivity with two doses,  
22 maybe in boot camp, that will work and be very, very favorable.  
23 And I think their follow-up 40,000 patient review of data going  
24 forward, it actually makes a lot of sense. But certainly for  
25 the military, short-term vaccination is very, very important.

1 Thank you very much.

2 DR. EDWARDS: Thank you, Dr. Woody.

3 The next is Rhea Racho. Rhea Racho.

4 (No response.)

5 DR. EDWARDS: The next is Bunmi Daramaja.

6 MS. DARAMAJA: Good afternoon, everyone. I want to say  
7 thank you to the Advisory Committee for, you know, giving us a  
8 courtesy to listen to our concerns.

9 Today is kind of a memorial day for me and also a day of  
10 hope. My dad died from hepatoma today, 1995. He would've been  
11 87 years old. And my brother died from hepatoma. He would  
12 have been 50 years old this month. It's kind of a sensitive,  
13 you know, month for me when you lose someone that you love from  
14 a disease that is preventable. There's so many lives that this  
15 monster virus have destroyed all around the world. But in lieu  
16 of waiting for a cure, there's -- we have vaccines out there  
17 that are saving lives.

18 I'm here today to speak as a pharmacist and as someone who  
19 understands the importance of compliance. The current vaccines  
20 we have, have saved lives, but some studies show that an  
21 average of 54% of the adults who receive these vaccines  
22 complete the series. So why wouldn't we jump hooray when we  
23 hear another vaccine out there, you know, that you give two  
24 doses within 1 month that will save more lives.

25 As a pharmacist, one of the great accomplishments that we

1 have is when you have a patient who is very compliant, you  
2 know, with taking their medications. When we give these  
3 vaccinations and there are supposed to be three doses and you  
4 have to hunt them down, the patients, you know, to complete  
5 their series, it's not fun at all; some will not even show up.

6 I will read some statements from some of the pharmacists  
7 that I discussed this with, and one of them said, and I  
8 quote --

9 DR. EDWARDS: I think we need just one more comment and  
10 then your time has run out.

11 MS. DARAMAJA: Okay. One of them said, "I will highly  
12 prefer a two-dose that is offered in a shorter amount of time,  
13 especially if efficacy is equivalent and covered by insurances.  
14 My main reason is compliance issues regarding three doses over  
15 a long period of time."

16 And I thank Dynavax for their effort in making this  
17 vaccination to save more lives. It will be a great  
18 accomplishment for we pharmacists when we can report that 95%  
19 of the patients that we do vaccinate, you know, receive the  
20 complete doses.

21 DR. EDWARDS: Thank you.

22 MS. DARAMAJA: Thank you very much.

23 DR. EDWARDS: Thank you very much.

24 Jason Crum.

25 (No response.)

1 DR. EDWARDS: Maureen Kamischke.

2 MS. KAMISCHKE: Hello. I have no conflicts, and my  
3 perspective is personal.

4 I'm the parent of a child adopted from China. She came to  
5 us with hepatitis B. As you know, it's typically a very  
6 asymptomatic disease in children, but unfortunately that wasn't  
7 the case with my daughter. By the age of 4, she had  
8 experienced multiple liver biopsies, treatment with interferon  
9 and antivirals and significant liver damage. There was even  
10 talk of a liver transplant in her future, but fortunately that  
11 never happened.

12 There's been an effective vaccine, you know, for decades,  
13 and of course, we wish our daughter had benefited from a birth  
14 dose of the vaccine, but there were other obstacles in our  
15 family that we had to deal with. When we came home and learned  
16 of her infection, we confirmed immunity of family members only  
17 to learn that my husband did not have adequate titers.  
18 Grandparents were involved, and they wanted to be ensured that  
19 they were protected.

20 Unfortunately, the currently available vaccines are not as  
21 effective in older, overweight, or adults that have any  
22 autoimmune issues. The series entails three shots in 6 months  
23 to complete, and that really feels like a lifetime when you're  
24 worried about exposure to a baby covered in open sores and with  
25 a high viral load.

1           Today my job entails working with people living with  
2 chronic hepatitis B. People live with chronic hep-B, they fall  
3 in love and they want to live a normal life, and yet, waiting 6  
4 months plus a month or two to confirm immunity is just a little  
5 bit too long. Some are not able to generate an immune response  
6 even after two complete series, so what are they supposed to  
7 do? Marriage proposals are broken, and there's panic and  
8 there's shame about their hepatitis B infection.

9           There are numerous reasons why a current three-shot  
10 vaccine series isn't completed and why there are so many that  
11 remain unprotected. The availability of a safe and effective  
12 two-shot vaccine series, which can be administered within a  
13 month, is critical to the elimination of hepatitis B by 2030 in  
14 both the U.S. and around the globe.

15           Thank you.

16           DR. EDWARDS: Thank you.

17           The final speaker will be Michael Weir.

18           MR. WEIR: How are you doing? I have no conflicts. Good  
19 afternoon. My name is Mike Weir, Manager for Policy and  
20 Legislative Affairs at NASTAD. NASTAD is a leading  
21 nonpartisan, nonprofit association that represents public  
22 health officials who administer HIV and hepatitis programs in  
23 the U.S. and around the world. Our singular mission is to end  
24 the intersecting epidemics of HIV, hepatitis, and related  
25 conditions. We do this work by strengthening domestic and



1 global governmental public health through advocacy, capacity  
2 building, and social justice.

3 For many years our members have been concerned about low  
4 hepatitis B vaccination rates among adults at risk, including  
5 gay and bisexual men, people who inject drugs, and persons  
6 living with HIV. As a nation, we must prioritize resources and  
7 public health action to ensure that every adult at risk has  
8 access to hepatitis B vaccination. We urge the FDA to approve  
9 this two-dose vaccine, which will be an important addition to  
10 our prevention arsenal.

11 Public health leaders have identified a variety of reasons  
12 for low adult hepatitis B vaccine coverage: low public  
13 awareness, clinics not stocking that vaccine or the vaccine,  
14 and even concern about losing clients over the lengthy three-  
15 dose schedule. FDA approval of a two-dose hepatitis B vaccine  
16 will create new attention and awareness of the need for  
17 vaccination and ensure a more efficient series completion for  
18 providers and consumers.

19 As the opioid epidemic continues across our country, new  
20 cases of hepatitis B and C as well as HIV are emerging. The  
21 availability of a two-dose hepatitis B vaccine will help  
22 clinicians and public health providers prevent new infections  
23 among susceptible adults.

24 Similarly, the availability of a two-dose vaccine will  
25 increase series completion in clinical and public health

1 settings which serve gay and bisexual men, people living with  
2 HIV, and people who inject drugs, the populations experiencing  
3 the highest rates of new infections.

4       The *National Strategy for the Elimination of Hepatitis B*  
5 *and C: Phase Two Report* highlights that we can eliminate  
6 hepatitis B in the U.S. The inclusion of a two-dose hepatitis  
7 B vaccine will assist in national, state, and local efforts to  
8 achieve this goal.

9       Thank you for your consideration of our comments. Thank  
10 you.

11       DR. EDWARDS: Thank you. Are there any other speakers?  
12 Please. Introduce yourself.

13       DR. YOUNG: Thank you. I'm Dr. Sherri Young from the West  
14 Virginia Bureau for Public Health. I have no financial  
15 disclosures, and I have no conflicts of interest.

16       I come here to you from West Virginia today because we are  
17 number one in hepatitis B. Not only are we number one in  
18 hepatitis B with an incidence of 14.5 per 100,000 patients, we  
19 are 15 times the national average as far as hepatitis B  
20 incidence in our state. Most of those are identified between  
21 the age of 30 to 44, so we do have a heavy burden in our adult  
22 population. In addition to that, we do identify multiple risk  
23 factors.

24       Along with the other public health officials that I've  
25 heard here today, IV drug abuse is thought to be one of the

1 biggest risk factors that we have. Again, we're also number  
2 one in overdose deaths in the state of West Virginia. So I  
3 appreciate you listening to our plight today.

4 What we are excited about is the fact that we have the  
5 availability or potential availability of a two-dose hepatitis  
6 B vaccine with good efficacy seen with two doses 4 weeks apart,  
7 because that could be used in our syringe exchange programs, it  
8 could be used in our harm reduction programs, and it could be  
9 used to focus on our adult population so that maybe we will be  
10 number one in something other than hepatitis B and drug  
11 overdose deaths at some point.

12 I thank you for listening.

13 DR. EDWARDS: Thank you very much.

14 Are there any other speakers for the Open Public Hearing?

15 (No response.)

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

17 So now it's time to go over and address our questions. Do  
18 we want to have the questions put on the -- please.

19 DR. WHARTON: Could I ask if there are any data about the  
20 use of this vaccine in persons who had already received one or  
21 more doses of one of the currently licensed vaccines?

22 DR. JANSSEN: No, we haven't systematically studied that.  
23 We anticipate looking at that in the postmarketing study.

24 DR. LEVY: Sorry, another quick question.

25 DR. EDWARDS: Yes. Please, Ofer.

1 DR. LEVY: Can Dynavax comment on the manufacture of the  
2 Heplisav lots across these studies? Was there any change in  
3 the standard operating procedure or quality of the vaccine?

4 DR. JANSSEN: No, there were no changes in the specs. The  
5 vaccine intended for commercial -- for sales is the same  
6 vaccine that's been used throughout.

7 DR. EDWARDS: Yes, Dr. Packer.

8 DR. PACKER: Yeah, I'm sure everyone knows the answer to  
9 this except me, but if someone gets two doses of the currently  
10 available vaccine and does not have sufficient titers, does  
11 that mean that they are not protected against hepatitis B?

12 DR. EDWARDS: Probably. I think that the immune response,  
13 after three doses, isn't 100%.

14 DR. PACKER: But I heard at the beginning that after years  
15 the serum titers go down and yet there's still protection.

16 DR. WARD: That's correct, that's correct. That's  
17 correct.

18 DR. EDWARDS: But that's in the face --

19 DR. WARD: If they had it documented --

20 DR. EDWARDS: -- response.

21 DR. WARD: -- serum conversion greater than 10, even if  
22 they fall below that in the future, they're considered to be  
23 protected in the typical situation outside of  
24 immunosuppression.

25 DR. PACKER: I understand that titers are a surrogate

1 endpoint, but what I'm trying to figure out is just because  
2 someone gets two doses of a conventional vaccine, does that  
3 mean they're not protected?

4 DR. HOOFNAGLE: One issue is whether it's neutralizing  
5 immunity or whether it's immunity that prevents chronicity or  
6 severe disease, and I'm afraid that's not really answered. But  
7 one issue is that people who receive the vaccine may be  
8 partially protected, you see. So in long-term follow-up of  
9 vaccinated children, for instance, you find evidence of some of  
10 them actually became infected with hepatitis B, they develop  
11 anti-core, but there's no carrier, right? Am I right, John, on  
12 that?

13 DR. WARD: There's no clinical disease, typically, either.  
14 So it's not a sterilizing vaccine.

15 DR. HOOFNAGLE: It prevents clinical disease.

16 DR. PACKER: If I only got two doses of the current  
17 vaccine and didn't come back for my third, would you say I was  
18 okay?

19 DR. HOOFNAGLE: I wouldn't say it publicly, no.

20 (Laughter.)

21 DR. HOOFNAGLE: But this is one question I have --

22 DR. PACKER: I'm trying to make this --

23 I'm sorry, I'm trying to make this understandable to the  
24 cardiologists.

25 DR. HOOFNAGLE: Have you used this vaccine to try to boost

1 titers or try to give it to people who have failed the standard  
2 vaccine?

3 DR. PACKER: I just want to know if the people who have  
4 failed the standard vaccine are still at risk of hepatitis B.

5 DR. WARD: Yes.

6 DR. EDWARDS: Yes.

7 DR. HOOFNAGLE: Yes.

8 DR. PACKER: We know that?

9 DR. WARD: The proportion that reach that 10 level --

10 DR. PACKER: I understand. I just want to know if I fall  
11 below the 10 level --

12 DR. WARD: After reaching it.

13 DR. PACKER: No, no. I never reach it.

14 DR. WARD: Then you're considered susceptible.

15 DR. PACKER: Do we have data that says I am?

16 DR. WARD: In the older studies, yes.

17 DR. HOOFNAGLE: Very old.

18 DR. WARD: Very old studies, the original studies, yes.

19 DR. JANSSEN: So we haven't looked -- again, we haven't  
20 looked at current vaccines with respect to Heplisav. If we  
21 gave a third dose, we really increase our GMCs a lot, but we  
22 haven't systematically looked at after Engerix or after  
23 Recombivax.

24 DR. HOOFNAGLE: So one question is whether after you prime  
25 people with this vaccine that turns on your dendritic cells,

1 you need to give it again or can you get away with the standard  
2 alum-induced thing? So the experiment would be is to give --

3 DR. JANSSEN: Yeah.

4 DR. HOOFNAGLE: -- as three groups, you understand?

5 DR. JANSSEN: Right. No, we've never done that study.

6 No. I will say, though, in young people, in people in their  
7 20s, 80% of them had antibody levels over 10 after one dose.

8 DR. HOOFNAGLE: Have you done the experiment?

9 DR. JANSSEN: Not the experiment you're talking about.

10 DR. HOOFNAGLE: You must have done the experiment in mice  
11 or something, right?

12 DR. JANSSEN: No.

13 DR. HOOFNAGLE: No?

14 DR. COFFMAN: The experiment to come to --

15 MR. HOOFNAGLE: One dose of your vaccine and then the  
16 second dose with either your vaccine or the standard.

17 DR. COFFMAN: Actually, I can't think of a situation with  
18 any antigen where we've really done that experiment. We've  
19 kind of done it the other way around for different antigens,  
20 not for hepatitis B, but we've not done it in that order, so I  
21 can't answer the question.

22 DR. EDWARDS: And you haven't done any studies of people  
23 who have not responded to other standard hepatitis vaccines?

24 DR. JANSSEN: Not systematically, no.

25 DR. EDWARDS: Other questions before we begin to discuss

1 the specific questions that are addressed? Any context  
2 questions or issues that people have that --

3 (No response.)

4 DR. EDWARDS: So then let's go ahead and begin to address  
5 the questions that we are being asked. The first question is  
6 "Do the available data support the safety of Heplisav when  
7 administered to adults 18 years and older?"

8 What I would like to propose is that we go around the  
9 table and people discuss their thoughts, and then after we do  
10 that, then we will vote on this question.

11 Yes, Dr. Packer.

12 DR. PACKER: I didn't want to interrupt. I just wanted to  
13 ask, this is a binary question?

14 DR. EDWARDS: That is -- well, that is a question that we  
15 are asked to vote yes or no; however, if we vote yes, we are  
16 expected to comment on the pharmacovigilance plan. If we vote  
17 no, then we are asked to specify which groups might be included  
18 or excluded.

19 DR. PACKER: But it is possible to vote no --

20 DR. EDWARDS: Correct.

21 DR. PACKER: -- and want to comment on the  
22 pharmacovigilance plan?

23 DR. EDWARDS: It's really possible for you to do whatever  
24 you'd like.

25 DR. PACKER: Okay.



1 (Laughter.)

2 UNIDENTIFIED SPEAKER: That's embarrassing.

3 (Laughter.)

4 DR. EDWARDS: Okay. So let's start, since we have a lot  
5 of activity down here, let's start with Dr. Lee, and would you  
6 like to comment on your thoughts about the first question, "Do  
7 the available data support the safety when administered to  
8 adults 18 years and older?"

9 DR. LEE: Well, from the data, it looks it needs more  
10 work, but if it pass, I hope the prospective study will have a  
11 better monitor with planned interim analysis with stopping rule  
12 to make sure they won't have too much, too many adverse events,  
13 like acute MI. And also in the prospective study, like a  
14 better, I mean, more detailed time-to-event analysis may be  
15 needed, but right now it looks like -- because all the analyses  
16 were frequency of the event, so it's difficult for me to make a  
17 conclusion. Thank you

18 DR. EDWARDS: Yes?

19 (Off microphone question.)

20 DR. EDWARDS: Please.

21 DR. DE GRUTTOLA: In the interest of time, the quickest is  
22 just to show Slide AA-20, which compares the -- Victor De  
23 Gruttola, Department of Biostatistics, Harvard School of Public  
24 Health. I've worked in clinical trials for 30 years.

25 And this slide demonstrates both a contingency table

1 analysis and time-to-event analysis, which is a hazard ratio  
2 from Cox proportional hazards, both types of analyses were  
3 done, and as you can see, the 95% confidence intervals and the  
4 point estimates themselves are very close and just go -- this  
5 slide is looking at the adjudicated MACE in the pooled dataset,  
6 and the next slide, 21, presents the analyses for MACE just in  
7 HBV-23. And once again, these results are very similar.  
8 Analyses were also done just for acute MI, similar results.

9 DR. LEE: Thank you, Victor. But still, those results for  
10 MI are kind of inconclusive.

11 DR. EDWARDS: Dr. Packer.

12 DR. PACKER: So actually, I mean, we can talk about this  
13 for a very long time but -- and we have, and I guess we could  
14 continue. We're not going to know the answer to the myocardial  
15 infarction issue. We are just not going to know.

16 So my difficulty with the question as phrased is do the  
17 available data support the safety? And the problem is that  
18 that's really not how you decide whether a drug should be made  
19 available or not. It's benefit-risk, what do you get versus  
20 what the risk is. And so every drug which is presumably on the  
21 market has a benefit-risk relationship in someone's favor, and  
22 that doesn't mean it is risk free. Every drug on the market  
23 has safety issues.

24 So it's hard to answer a question, "Do the available data  
25 support the safety?" Well, the answer is, well, if I asked

1 that question for every drug, I would say it depends on how  
2 pure you want that to be.

3 My own personal sense is that if the FDA, if this  
4 Committee, if the FDA and if the Sponsor agree to put into  
5 labeling a description of the imbalance in myocardial  
6 infarction events, then that would fully describe the  
7 uncertainty that exists, and I would allow a vaccine like this  
8 to go forward and would allow people who use the vaccine to at  
9 least be aware of what was seen in the clinical trials.

10 DR. EDWARDS: Thank you.

11 Dr. Gruber, did you have a comment?

12 DR. GRUBER: I just wanted to comment, yes. I mean, I  
13 think the earlier FDA sort of elaborated that we've had an  
14 Advisory Committee where we, you know, asked about would the  
15 data support the effectiveness of Heplisav, and the other  
16 question was at that time would the available data support the  
17 safety? Of course, it is clear that it is always a risk-  
18 benefit decision. We would never ask the Committee to only  
19 opine on the safety.

20 But since that question already had been asked in 2012 and  
21 today these data were reviewed not only by Dynavax but also by  
22 the FDA, you know, we didn't think we had to ask that question  
23 over again, and I hope that was clear.

24 Point well taken, it's always a risk-benefit decision, but  
25 I'm also understanding Dr. Packer to say, you know, it depends

1 what the FDA will write into the labeling, in other words,  
2 education, describing this imbalance, etc. Are you saying that  
3 you would then go forward and say that available data support  
4 the safety in adults 18 years and older?

5 DR. PACKER: If I could rewrite the question, which I know  
6 I can't do, right, but I would -- there's nothing here that  
7 allows one to definitively say that there -- you know, there  
8 isn't a risk of myocardial infarction; there may be a risk,  
9 there may, in fact, be a likely risk, but the question -- I  
10 mean, I would favor approving the vaccine as long as what was  
11 known about the myocardial infarctions was actually included in  
12 the labeling. That way you allow the uncertainty to be fully  
13 expressed to the public. I don't understand why we have to  
14 reach decisions about certainty when such -- when uncertainty  
15 is the only reality. So I would just fully describe the  
16 uncertainty.

17 DR. EDWARDS: Thank you.

18 Dr. McInnes.

19 DR. McINNES: So I think this is a very exciting vaccine.  
20 It's already been in development for -- and testing for quite  
21 some time. The issue about the number of doses is really very  
22 attractive. I think the immunogenicity profile is impressive.  
23 There are imbalances in ischemic cardiac events in the HBV-23  
24 study. I think despite all good efforts, the causal  
25 interpretation remains limited.

1           The data have been massaged, and I don't mean  
2 disingenuously, I mean honestly, as best they can be, and I  
3 think we've mined them for what we can get out of them, and  
4 they are what they are. I think the analyses that were  
5 presented are reasonable, but as somebody who has to now make a  
6 decision in myself how I feel about this, I'm left that this  
7 really could be a real observation, and I can't come out with a  
8 construct to discount that. So this gives me pause.

9           I am of the opinion that this needs further study. As  
10 much as I want to be assured, I'm not comforted by the plans I  
11 heard concerning the Kaiser study, and I think it would've been  
12 extremely helpful to have understood a little bit more clearly  
13 what might be gained from that and how certain we might become  
14 in a relatively short period of time, should this be licensed,  
15 about what the risk really is.

16           So those are my comments. Thank you.

17           DR. EDWARDS: Thank you.

18           Dr. Levy.

19           DR. LEVY: I guess I would start by saluting Dynavax  
20 because I know they've been at this for a very long time, and  
21 you know, we spend most of the time worried about this  
22 potential safety signal, this MI, but you know, not only is  
23 this adjuvanted vaccine effective, it's super-effective. I  
24 mean, if you look at the data compared to the vaccine we have  
25 now, it's not even close. This thing blows it out of the

1 water. And the number of dose issue is huge, and getting  
2 strong immune responses in older individuals is huge. Vaccinal  
3 antigens tend to be expensive, so if you can have an  
4 adjuvant -- so for a lot of reasons, I'm very excited about  
5 this vaccine.

6 I'll try not to rehash what other people have said. It's  
7 hard to exclude that there's some signal there for MI, and I  
8 think this should move forward, but any way it moves forward,  
9 there needs to be some sort of evaluation that that's  
10 meticulous with some sort of design that allows a rapid  
11 identification of a signal if it's verified.

12 So I think most of the data we saw did support safety, but  
13 that one piece that all the committee members thus far have  
14 commented on is the unknown, and now the question in front of  
15 us is what is a rational way to follow up on that in a  
16 responsible and meticulous way without throwing the baby out  
17 with the bathwater?

18 DR. EDWARDS: Thank you.

19 Dr. Kotloff.

20 DR. KOTLOFF: Well, it's interesting. I think a very  
21 consistent picture is coming through, and I pretty much am in  
22 line with the comments that I've heard. I think that there is  
23 a place for this vaccine. It has very impressive performance  
24 in generating high antibody levels after fewer doses, but I  
25 think that we haven't heard convincing evidence that there

1 isn't convincing evidence yet that it might not be associated  
2 with myocardial infarction and also with rare autoimmune  
3 events. I think both of those issues are in play.

4 I think that doing post-licensure surveillance and doing  
5 an adequate job at trying to sort this out post-licensure will  
6 be extremely difficult, for one, because the risk group that  
7 we're worried about may -- will be hard to do the study in that  
8 group. And two, the problem with the existing vaccines is that  
9 people aren't compliant, and to do a really good study you need  
10 to have a fair amount of compliance. But I think that there  
11 should be a lot of attention in trying to develop a very good  
12 postmarketing vaccine plan.

13 Thanks.

14 DR. EDWARDS: Dr. Sawyer.

15 DR. SAWYER: I will echo the previous comments, including  
16 the one that answering this binary question is a challenge. I  
17 think, though, that there is a reasonable chance that this  
18 myocardial infarction signal is spurious based on the multiple  
19 variables that were looked for and the lack of a temporal  
20 association that we've gone over.

21 So I do think the benefit outweighs the current assessment  
22 of the risk, but as I'm sure we'll discuss in a minute in the  
23 subsequent questions, I, too, am very concerned about the  
24 design of the postmarketing study. It needs to be able to  
25 answer the question, and it needs to be able to answer it

1 quickly, and I think as proposed, it might not do that.

2 DR. EDWARDS: Thank you.

3 Dr. Portnoy, would you like to comment on this question?

4 DR. PORTNOY: I would, thank you. Can you hear me okay?

5 DR. EDWARDS: Yes, very well. Thank you.

6 DR. PORTNOY: Thank you. And thank you for letting me  
7 participate in this event by telephone. I had surgery 2 weeks  
8 ago, and my doctor didn't want me to travel, so thank you for  
9 accommodating that.

10 I would vote yes on this question. I think that the  
11 safety of the data are reassuring. The company has clearly  
12 addressed the issues that were raised in the previous  
13 submission.

14 In my opinion, part of the safety includes the fact that  
15 it is extremely effective. I think it's not safe to be at risk  
16 of getting hepatitis B. It's safer to get the vaccine than to  
17 be at risk of hepatitis B, so the risk-benefit is what I look  
18 at. The improved schedule will also improve compliance.

19 My only concern, of course, is the signal that we've all  
20 talked about for the cardiovascular events such as MI. I  
21 suggest that the package insert include a warning or some kind  
22 of alert for individuals who have increased cardiovascular risk  
23 factors. Perhaps increased attention should be paid to those  
24 individuals, or perhaps they should be instructed to get the  
25 other vaccine.



1           The immunologic and autoimmune adverse events don't seem  
2 to be greater than -- with the new product than with other  
3 vaccines. All vaccines seem to have at least a minor risk of  
4 having those problems, so I'm not overly concerned about those.

5           Basically, I just don't think it would be right to  
6 withhold this vaccine from the millions of people who could  
7 benefit with it because some people have risk factors for MI.  
8 Those people could be managed in a more specific approach.

9           The proposed surveillance program is good, though as  
10 everyone has mentioned, I'm not convinced that the patients  
11 will be allocated in an unbiased manner. Patients with  
12 cardiovascular issues might be just sent to a different clinic  
13 to get the other vaccine perhaps. I suggest asking the medical  
14 community in general, the whole national community, to be more  
15 vigilant in reporting any AEs that might occur in association  
16 with the vaccine, perhaps through marketing materials that the  
17 company puts out when they promote this vaccine. There should  
18 also be instructions on how to actually report an AE because  
19 not all physicians know how to do that. When the reports come  
20 in, the FDA should probably pay closer attention to those  
21 particular reports.

22           So those are my thoughts.

23           DR. EDWARDS: Thank you very much.

24           I'm Kathy Edwards. I agree that this is difficult to  
25 address in yes or no. The available data that do exist have

1 been looked at in very meticulous and comprehensive ways and  
2 have been thought about and really dissected in an admirable  
3 way, but certainly as Dr. Packer said, it still does leave  
4 questions. But as Mark said, it does also suggest that maybe  
5 it is spurious, and so I think it is very confusing indeed.

6 I think the impact of a two-dose schedule, particularly  
7 with this potent adjuvant, would immunize effectively many more  
8 people than we are currently. However, I am pretty dismayed  
9 about the proposed pharmacovigilance plan, and I think it needs  
10 to be more comprehensive, I think it needs to think about how  
11 patients will be allocated, how patients will be followed, how  
12 the vaccine will be distributed, whether it will only be able  
13 to be accomplished in one setting and really needs to -- a lot  
14 more information and details to allow me to feel comfortable  
15 with a yes.

16 DR. GRIFFIN: Yeah, so --

17 DR. EDWARDS: Dr. Griffin.

18 DR. GRIFFIN: Thanks. So I'm going to vote yes. I'm  
19 comfortable that the study really addressed the concerns of the  
20 2012 Committee adequately, that HBV-23, I thought, laid some of  
21 those concerns -- much lower level. There's this new concern  
22 about MI, but I think that was unanticipated.

23 I don't think -- usually, you can find good biologic  
24 plausibility for just about anything, but I think the temporal  
25 association, the biologic plausibility for this association, is

1 not strong.

2 I think if we spend a lot of time on the prostate cancer  
3 and -- where we saw the very opposite thing, you know, if  
4 things were different, we might be very concerned about  
5 prostate cancer in Engerix.

6 So I think it's, you know, no one knows obviously, and we  
7 won't get an answer. And like everyone else, I think the  
8 postmarketing study will be very important not only for this  
9 vaccine but for the adjuvant and for using it going forward,  
10 especially in people who are at risk for -- elderly people who  
11 are all going to be at risk for cardiovascular events. So I'm  
12 not sure we want it to be something where it's set up so that  
13 people at risk for cardiovascular events are excluded.

14 DR. WHARTON: So I think probably everything I'm going to  
15 say somebody else has already said. It's very exciting to have  
16 a vaccine with these characteristics at this point in  
17 development, and it seems to me that the available data allow  
18 it to move forward.

19 That doesn't mean that all of the issues have been fully  
20 addressed. Clearly, there was this unanticipated imbalance  
21 around acute myocardial infarction, which, you know, really  
22 didn't make any sense based on earlier experience or what we  
23 think about how the components of this vaccine work and what we  
24 understand about how myocardial infarctions happen and the  
25 timing, where are really -- the divergence was a 100 days out,

1 and it's hard to put all that together in any way that raises a  
2 higher level of concern.

3         So I think it's something that can't be dismissed, it has  
4 to be addressed. My own feeling is it can be addressed post-  
5 licensure. I have not heard enough about the post-licensure  
6 plans to make me confident that right now there is a plan that  
7 will fully do that, but I believe that plan can be developed.  
8 I just don't know that it has been yet. And clearly, post-  
9 licensure surveillance is going to be important for the kind of  
10 rare autoimmune conditions that cannot be ruled out that we  
11 still might see post-licensure with wide disparate use of the  
12 vaccine.

13         So I will vote yes when the time comes to hit the button,  
14 but there clearly will need to be additional work done.

15         DR. EDWARDS: Dr. Monto.

16         DR. MONTO: I'm not going to repeat all of the wise words  
17 that we've heard. My initial reaction when I saw the results  
18 in reviewing the material was that this was spurious because  
19 we -- those of us who do studies always worry about something  
20 like that coming up, but I wish it were not so spurious, so  
21 unbalanced. I mean, I think that's what's troubling. The  
22 results really were very unbalanced, and the probability of  
23 that happening is a bit of a worry.

24         I'm a bit uncomfortable in voting in the order that we're  
25 voting because I would be comfortable given the superiority,

1 and I know it's -- this was not a superiority endpoint. In  
2 voting, I would be much more comfortable voting yes if I knew  
3 what the pharmacovigilance study was and that it would not  
4 result in the kind of label that would result in nonuse in just  
5 the populations where it should be used, and that's my major  
6 concern.

7 I think this is a vaccine we want to see used, and I think  
8 we need to take into consideration whether voting yes and then  
9 talking about pharmacovigilance is better than voting no and  
10 then approving for a specific population, which is the other  
11 question and one I ask for guidance on. And I think we really  
12 need to choose between two not-too-comfortable decisions.

13 DR. EDWARDS: Ruth. I think we need to finish before --  
14 thank you.

15 DR. LYNFIELD: I guess, whether it's an advantage or  
16 disadvantage sitting at this end of the table, I think  
17 everything's been said. I agree particularly with the last few  
18 speakers. I do think that it probably is spurious; I think  
19 that it would be very important to have a very robust  
20 pharmacovigilance plan, as people have articulated, and perhaps  
21 after we go around the table, could we talk a bit in greater  
22 detail, I think that would be very useful, about what that  
23 pharmacovigilance plan would be?

24 But, you know, again, as everyone said, it's a very  
25 exciting vaccine and, you know, let's keep an eye on the big

1 picture and the lives that we can save.

2 DR. EDWARDS: Dr. Englund.

3 DR. ENGLUND: Yes. I would just like to say I agree. I  
4 think this is an important vaccine. I work in the field of  
5 transplantation. We need this vaccine to save lives, and we  
6 can't wait 10 years to get something like this. I truly feel  
7 we need it, we need it.

8 I think we have to judge this as a risk versus benefit and  
9 there is the imbalance of MI, which may or may not be real, and  
10 there's an imbalance of seroprotection, which people who get  
11 infected with hepatitis B have incredibly high rates of serious  
12 disease and even fatal disease.

13 So I am very much in favor of this, and I think the FDA  
14 has a history of helping design postmarketing trials, and they  
15 know how to do that, and we should empower them. We can give  
16 them ideas, but we should empower them that that should be part  
17 of the deal.

18 DR. EDWARDS: Thank you.

19 Dr. Bennink.

20 DR. BENNINK: Yeah, I'll try to keep it short because I  
21 think great comments have been made. But I think in terms of  
22 the postmarket, we don't know all the details. But I still  
23 think I would be more in favor, even though I know it's  
24 difficult, in addition to whatever they were doing there, to do  
25 something that was more targeted toward the myocardial risk

1 group and try -- even if it's small or something like this, and  
2 try to prospectively really follow them in some way that may  
3 tell you that there's risk coming in before they, in some  
4 respects, even have problems or before it really becomes death  
5 or something like this. So I would say along that line, you  
6 know, we don't know; it may be spurious, it may be something  
7 else.

8 I would also make a little bit of a comment that I think  
9 Dr. Packer made the comment, that atherosclerosis is  
10 inflammation, and therefore even though it's different than  
11 what we typically think of, and maybe this is because innate  
12 immunity is becoming so much more studied and everything else,  
13 it is immune mediated, from that perspective. It's not what  
14 you're thinking about in terms of autoimmunity or something  
15 else, but it is immune mediated.

16 DR. EDWARDS: Dr. Hoofnagle.

17 DR. HOOFNAGLE: Yes, well, I agree that this is a real  
18 advance for hepatitis B. It's something that's been defined in  
19 the past as a great need, a better vaccine, more potent, and  
20 also given in fewer doses, so that's completely clear.

21 The problem here is that we're not really dealing with  
22 approval of a hepatitis B vaccine so much as approval of an  
23 adjuvant. A new adjuvant, as I understand, would be the first  
24 in human use approved. So that's really the issue; that's  
25 where the safety comes up.

1           But that puts a greater burden on you because this is not  
2 going to be the last use of adjuvants that interact with the  
3 toll-like receptors; I suspect more and more are going to come.  
4 So that's why I think it's very critical that this issue be  
5 addressed directly and answered. And so I would vote yes for  
6 this vaccine.

7           But I'd also ask the FDA to basically request a study  
8 specifically focused on myocardial infarction. If you do  
9 another big study of 20,000, 40,000 people, something else is  
10 going to show up as different between the groups. This time it  
11 will be breast cancer or something worse. But I think this,  
12 what's been found so far, really needs to be addressed directly  
13 and maybe in a focused study rather than a global study.

14           DR. EDWARDS: Thank you.

15           Dr. Ward.

16           DR. WARD: Thank you. Well, as a member of the Committee,  
17 I just wanted to verify and second a lot of the comments that  
18 have been made by the Sponsors or by the members of the  
19 audience regarding the public health need for this vaccine and  
20 how we do have to balance benefits and risk.

21           You know, as was mentioned, we do have a problem with  
22 incidence of new hepatitis B infections in this country.  
23 They're among older adults who are -- immunosenescence is a  
24 real problem with the current vaccines, and they happen among  
25 populations where a three-dose schedule is really problematic.



1 We've heard some data from both of those audiences about the  
2 problems going from the second to the third dose.

3 The other issue is about when vaccine series is not  
4 started at all because of the complexity of that three-dose  
5 series for those settings where these marginalized populations  
6 are at highest risk for hepatitis B or are getting care when  
7 they do access the healthcare system. So there's a strong  
8 public health need for this type of vaccine, I think, that can  
9 be filled by this hepatitis B vaccine, but it has to be a safe  
10 vaccine.

11 And I think, you know, when looking over the data and  
12 hearing the presentations, I think the questions that were  
13 raised about safety in the original studies had been adequately  
14 addressed, and I think those questions were resolved in the  
15 complete databases we've heard from the FDA presentation. And  
16 it's a very large number of study subjects when you look at all  
17 of those studies collectively.

18 The acute myocardial infarction, you know, was an  
19 unexpected finding; it was not the intent of the study to look  
20 at that question. I think the temporal association is really  
21 weak, and so I think it is an issue of concern which should not  
22 preclude the licensure of this vaccine.

23 So I think the vaccine data collectively demonstrate that  
24 this vaccine is safe enough to be licensed for use, and then we  
25 can have a discussion about whether we want to have any

1 populations of concern to be highlighted in the package insert  
2 and what are the proper designs of postmarketing surveillance  
3 after licensure.

4 Thank you.

5 DR. EDWARDS: Thank you.

6 Dr. Nolte.

7 DR. NOLTE: I don't have any comments.

8 DR. EDWARDS: Yes, Dr. Levy.

9 DR. LEVY: Yes. So something that Dr. Hoofnagle said kind  
10 of resonated with me and made me think of a very broad public  
11 health reason that it would be important as this moves forward  
12 to really nail a clear answer on the MI front, and that is  
13 that, you know, however this moves forward, and I hope it does,  
14 that FDA will have to consider that even if the association is  
15 spurious and even if postmarketing suggests that it's spurious,  
16 the better that point can be nailed down, the better it is for  
17 public health because what we don't want is a situation where  
18 there are a lot of vaccines in the world and a lot of  
19 myocardial infarctions in the world and there's a public  
20 perception of an associated risk.

21 Vaccines already, as you know, have suffered from  
22 inappropriate conclusions about autism, and the last thing the  
23 whole field needs is for elderly individuals -- so I just want  
24 to amplify what Dr. Hoofnagle said, that any postmarketing plan  
25 should be extremely rigorous to nail down that point.

1 DR. EDWARDS: Dr. Gruber, I wanted to bring up the  
2 question that Dr. Monto asked because it is -- if one answers  
3 yes to the first question, then that means for all populations,  
4 correct? Or do we -- go ahead.

5 DR. GRUBER: If the Committee were to answer yes for the  
6 first question, that would mean that that would be an  
7 indication in adults 18 years and older, that's what the  
8 indication would read, yes. If there -- well, I'm good at  
9 this. Yeah.

10 DR. EDWARDS: So in some ways it might be easier if we  
11 sort of incorporate Question 1 and 3; is that possible?  
12 Because we could say, you know, yes, we agree for all or no, we  
13 agree for all except this. But I'm happy to go as it's  
14 written, if that's how you prefer.

15 DR. GRUBER: Well, I'd like to make a point that the  
16 indication that the company seeks is really active immunization  
17 against, you know, infection in adults 18 years and older.  
18 That's the indication they would like to have in the package  
19 insert, and this is how we phrased the question. I very much  
20 hesitate to really reverse the sequence of the -- you know, of  
21 what we're asking here.

22 DR. EDWARDS: Good. Thank you for your clarity.

23 Okay, are there any more questions about or comments that  
24 people want to make about this first question? Yes, Dr. Monto.

25 DR. MONTA: You had mentioned having more discussion

1 before we vote about the pharmacovigilance because I think  
2 that's the thing that gives us some hesitation. The idea that  
3 we're not going to know for maybe 2½ years of use what the  
4 answer is about safety and the MI question gives you a little  
5 pause given the fact that there will be a move to use this in  
6 the population that needs it most. And if this doesn't happen,  
7 I've seen other situations where if there are questions  
8 involved when something new is launched, this just sort of  
9 lives with the product forever.

10 DR. EDWARDS: So I think that we do need to vote on the  
11 first question yes or no, but then I think we need to -- if  
12 yes, then I think that we will need to comment on the  
13 pharmacovigilance plan after a yes or no vote.

14 Yes?

15 DR. MONTO: We can't reverse that order?

16 DR. EDWARDS: Those are not the instructions that we  
17 received.

18 DR. MONTO: Okay.

19 DR. BENNINK: But could you -- excuse me. But could  
20 you -- if Arnold wants to discuss what those plans would be  
21 without any votes, what the committee members are thinking  
22 about a plan, the discussion about those plans, I mean, you  
23 don't think we should discuss those at all until there's a  
24 decision about 1?

25 DR. EDWARDS: I'm fine to hear other ideas or plans about

1 it.

2 Dr. Gruber, do you want us to do 1, or could we open the  
3 comments on the plan for 2? Would you prefer just to have us  
4 vote for 1 and then go on to 2 and 3 and 4?

5 DR. GRUBER: Well, I'd like to ask a question. Depending  
6 on the discussion of the pharmacovigilance, what I'm hearing is  
7 that somehow would influence how you vote on Question 1?

8 DR. BENNINK: Well, for some of the people who commented,  
9 that was my impression, that people wanted to hear about a  
10 robust pharmacovigilance plan.

11 DR. GRUBER: Right, but wouldn't you have the chance to  
12 comment on this when we discuss Number 2, "Comment on the  
13 proposed pharmacovigilance plan"? I mean, we put that point  
14 here for a reason because we, you know -- we agree that, you  
15 know, we have to have a robust discussion and really seek your  
16 input on what you heard today on the PVP and what you would  
17 like to see.

18 DR. SAWYER: I think what some of us would benefit from is  
19 clarification on the ability of FDA to work with the  
20 manufacturer on the details and to what extent can you dictate  
21 what is in the postmarketing study.

22 DR. MONTO: And particularly the timeline.

23 DR. LEVY: I guess, Dr. Gruber, our question is, does FDA  
24 have the power to make the approval contingent on a particular  
25 plan?

1 DR. GRUBER: We certainly, you know, have -- you know, can  
2 discuss or can request, you know, the pharmacovigilance plans  
3 to have certain elements, and we can also, you know, discuss --  
4 well, we have the authority to make it a required study versus,  
5 you know, a follow-up safety study; in other words, a  
6 postmarketing commitment versus a postmarketing requirement so  
7 that we can do -- but there is -- I mean, I think what I'm  
8 hearing, this is even a bit more complex. It's like what  
9 systems do we have in place to really, you know, look at this  
10 event versus what can the company do. I think we would have to  
11 have these discussions in particular, you know, if the  
12 Committee were to say we need to request, as was expressed by  
13 one of the committee members, we need to request for, you know,  
14 for the company to look specifically at the MI event.

15 So I think we have the authority to request, you know, for  
16 certain studies to be done, but I think it also depends, again,  
17 you know, what can we do given our existing systems and what  
18 the company will be able to do.

19 So I think we would have to have much more discussions,  
20 and I very much hesitate, really, here on the spot to tell you  
21 really yes or no, this can be done, this cannot be done. I  
22 invite, perhaps, my colleagues from the Office of Biostatistics  
23 and Epidemiology to weigh in here, if somebody wants to further  
24 elaborate on that.

25 (Off microphone response.)

1 DR. GRUBER: Yes, sure.

2 DR. EDWARDS: Dr. Sun.

3 DR. SUN: Hi, this is Wellington Sun. I'd just like to  
4 follow up Marion and maybe expand a little bit.

5 FDA has the authority to require certain types of  
6 postmarketing studies, and the process in which we do that is  
7 based on our interpretation of the data and working with the  
8 manufacturer to design the best study possible.

9 Now, I think there are limitations to what we can do even  
10 with the best of intentions, and that is the nature of  
11 postmarketing studies; for example, sometimes it's difficult to  
12 do a randomized controlled study at postmarketing.

13 So I think we have to recognize the feasibility of those  
14 types of studies in deciding, and that's one of the reasons why  
15 I think looking at studies, whether they're pre-licensure or  
16 post-licensure, is really important because the nature of those  
17 studies could be determined by whether it's a licensed product  
18 or pre-licensure. So I just want to sort of clarify that.

19 DR. EDWARDS: Dr. Kotloff and then Dr. Hoofnagle.

20 DR. KOTLOFF: I'm wondering whether our recommendation can  
21 include certain elements about the postmarketing surveillance.  
22 I don't think that we can design, here and now, a study that  
23 would be robust and satisfy it, but there could be certain  
24 elements, for example, that a study is required, that a study  
25 is designed that minimizes bias by doing appropriate allocation

1 to the two groups to examine the factors that we're concerned  
2 about, the events that we're concerned about, that the results  
3 be made available before 3 years' time, you know, within a  
4 certain time frame. So if we could just address what we think  
5 are the key elements.

6 DR. EDWARDS: Well, certainly that is -- 4 is a question  
7 that we're being asked, what additional studies are needed, so  
8 I think that we can address this.

9 Dr. Hoofnagle.

10 DR. HOOFNAGLE: Well, once a vaccine is made available,  
11 its use will depend on its cost, we haven't talked about that,  
12 and its perception of its safety, and if this vaccine is  
13 licensed with a big warning on it, this is a chance for them to  
14 erase that warning, is to do a study to show that that was --  
15 it was just happenstance, and with a critical prospective study  
16 this difference doesn't show up. So that's one way that the  
17 FDA has great influence on postmarketing studies: your product  
18 label.

19 DR. EDWARDS: Any other comments?

20 (No response.)

21 DR. EDWARDS: Okay, so we are being asked to vote yes or  
22 no, "Do the available data support the safety of Heplisav when  
23 administered to adults 18 years and older?" So a yes is a  
24 plus, a zero is an abstain, and a minus is a no. Vote now.

25 (Committee vote.)



1 DR. PORTNOY: And I e-mailed my vote to you already.

2 DR. EDWARDS: Could you also give a verbal vote, please?

3 DR. PORTNOY: Oh, I vote yes.

4 DR. EDWARDS: Please show the vote.

5 (Pause.)

6 DR. EDWARDS: They'd like us all to vote again, right?

7 Okay. Vote again, just like in Chicago, right?

8 (Committee vote.)

9 DR. PORTNOY: And again, I vote yes.

10 (Laughter.)

11 DR. EDWARDS: Eleven yeses, three abstains, and one no.

12 Okay, let's move now to -- oh. Okay, all right.

13 For the record, then, we want to vote -- to name the  
14 individual people who have voted for what -- so the greens or  
15 the yeses are Ward, Hoofnagle, Bennink, Englund, Lynfield,  
16 Monto, Wharton, Griffin, Edwards, Sawyer, and Kotloff.

17 Okay, there are three abstains, right? Three, let's see.  
18 And those are Levy, Packer, and Lee.

19 And McInnes, no.

20 Okay, so we'll now go to the second question: "Please  
21 comment on the proposed pharmacovigilance plan."

22 Dr. Lee, would you like to start, please?

23 DR. LEE: Yes. As we discussed earlier, it would be good  
24 to have a better plan to study -- for the prospective cohort  
25 study to include a different age group because, first, I'd like

1 to say, actually, I am for the approval of the -- of this  
2 vaccine. I'm not against it. Just as a statistician, I think  
3 the safety was not -- was inconclusive. But for the  
4 pharmacovigilance, the plan, I think it would be good to have,  
5 like, a specific subgroup analysis for the MI and also for  
6 other ratio study.

7 Thank you.

8 DR. EDWARDS: Okay.

9 Pam, do you want to go ahead, and then we'll get  
10 Dr. Packer --

11 DR. McINNES: No, given my vote, I would rather not go  
12 ahead.

13 DR. EDWARDS: Okay. Okay, good.

14 All right, Ofer.

15 DR. LEVY: We're asked to comment on the proposed --

16 DR. EDWARDS: Pharmacovigilance plan, yes.

17 DR. LEVY: Right. You know, I already did that several  
18 times.

19 DR. EDWARDS: Okay.

20 DR. LEVY: So, you know, I guess my question to FDA is  
21 then FDA does have the authority, Marion, to put the label, to  
22 put a label -- is that something that's been done in the past  
23 in this kind of setting?

24 DR. GRUBER: I mean, first of all, if safety events have  
25 been observed and it's regardless on what study or what vaccine

1 this is, we can, you know, describe those in labeling. But, in  
2 addition, we also have the authority to request certain  
3 postmarketing studies. We can -- you know, these PMR,  
4 postmarketing required studies, they, if you will, hold the  
5 company to a higher standard so that these studies need to be  
6 done, they need to be conducted. Postmarketing commitments are  
7 also studies that can be done, but it is more -- it's more like  
8 general additional safety data that need to be gathered.

9 So what this is going to be, I don't want to really decide  
10 here at the table, but we have the authority to request one or  
11 the other, okay? And that's contingent on some other issues,  
12 you know, prescribed by law, such as we have our own system,  
13 for instance, the Sentinel system. If we're not able to do  
14 these type of studies using that system, then it falls on the  
15 company to do, you know, a PMR. But yeah.

16 DR. EDWARDS: Karen, do you have any additional things  
17 that you haven't commented on about the proposed  
18 pharmacovigilance plan?

19 DR. KOTLOFF: I guess just a few specifics. One is that  
20 if the study were done at multiple sites, that you could have  
21 faster accrual and a quicker answer, that that would be an  
22 approach that I would think about. And then adequately powered  
23 for the age group at risk for MI. And then using the Sentinel  
24 surveillance systems for more longer-term surveillance looking  
25 at autoimmune. I think that's outside of what the company is

1 expected to do but what our existing systems might do.

2 DR. EDWARDS: Mark.

3 DR. SAWYER: Well, I think several people have articulated  
4 how important it is to understand this myocardial infarction  
5 connection, so I would suggest that whatever study be done is  
6 required, not just a commitment from the company. I think just  
7 letting it happen in Kaiser is fraught with some concerns about  
8 the age group that would be immunized and whether the Kaiser  
9 physicians would skew the use of the vaccine based on what is  
10 currently now public record about myocardial infarction. So I  
11 think a more scripted study is going to be required, and I  
12 would leave it to the FDA and the company to come up with what  
13 that looks like.

14 DR. EDWARDS: Dr. Packer, since you abstained, you really  
15 don't have to comment on the proposed pharmacovigilance plan,  
16 but we would welcome if you have comments.

17 DR. PACKER: The Sponsor has actually come up with a  
18 brilliant plan for such a study, which would be a cluster  
19 randomization at Kaiser. Essentially, certain Kaiser  
20 colleagues would only use one vaccine versus another on an  
21 exclusive basis. The actual assignment of that would be  
22 random.

23 The result of that would be a very low likelihood of major  
24 confounding, and it would make for an interpretable study that  
25 could go very, very quickly. If it's just a usual prospective

1 cohort study with choices being made, I think it's going to  
2 be -- they're going to get data which is going to be hard to  
3 interpret.

4 DR. EDWARDS: I think my comments about the proposed  
5 pharmacovigilance study, I already made several. I do think a  
6 couple things are really important. One is timeliness, so that  
7 if indeed we are concerned about this, and we are, then we want  
8 to make sure that we address this in as expeditious of a manner  
9 as possible, as Karen said, perhaps having many centers.

10 I think also the ability to look at, in a concentrated  
11 way, some of these patients using perhaps biomarkers or other  
12 sensitive assessments of cardiovascular function may also be  
13 helpful after the licensure as well, so I think that more  
14 detail about that as well.

15 Dr. Griffin.

16 DR. GRIFFIN: Yeah. I would agree that it should be a  
17 requirement rather than a commitment, and I mean, it would  
18 actually be more like a retrospective study if it was done as  
19 described unless someone collected data prospectively. There's  
20 data already in the EHR, but that's not considered a  
21 prospective study.

22 So I think the Sponsor and FDA might consider thinking  
23 about collecting cardiovascular risk factors prospectively to  
24 people who are getting both vaccines, so just to get a better  
25 level of detail for the analysis.

1 DR. EDWARDS: Dr. Wharton.

2 DR. WHARTON: The only additional comment I have is that  
3 consideration of an interim analysis plan that would allow  
4 either more timely reassurance or more timely identification of  
5 risk if they're identified.

6 DR. EDWARDS: Thank you.

7 Dr. Monto.

8 DR. MONTO: I certainly don't have any problems with  
9 observational studies since that's what we are mainly involved  
10 in right now. But I think my concern is the timeliness and the  
11 appropriate use of the vaccine in the populations in which you  
12 are most likely to see the events and given -- also, reliance  
13 on one area of the country and one health entity is sometimes a  
14 little risky. So if something else could be done, that would  
15 be, to me, helpful. And I think the timeliness is what is  
16 really going to be important because you just want to set this  
17 to rest as quickly as possible.

18 DR. EDWARDS: Dr. Lynfield.

19 DR. LYNFIELD: I agree with the comments that my  
20 colleagues have just made.

21 DR. EDWARDS: Dr. Englund.

22 DR. ENGLUND: I agree, too. I would like to just amplify  
23 two little things. When risk is mentioned, I really think that  
24 we need to be having an age limit or something. If we could  
25 design this -- I don't want to see 20,000 people between 20 and

1 40. I want to see 20,000 people between, you know, 50 and 70  
2 or 40 and 70.

3 So I really think -- I know that we've talked about  
4 cardiac risk, but really, if you just -- looking at the data  
5 they have, if you just did age risk, you really would be  
6 enriching for that population, and that's number one.

7 And number two, the comment was raised in the audience,  
8 and I noticed it when I was looking at it, is the Asian  
9 population is really minimal. This is, you know, 1 or 2%.  
10 It's really unfortunate, and I really -- we see this time and  
11 time again. The Sponsor should take this into account, when  
12 they design studies, that we should try the vaccine in the  
13 population it's going to be designed for. But California is a  
14 good place to do that so we can enhance the Asian population.

15 Thank you.

16 DR. EDWARDS: Dr. Bennink.

17 DR. BENNINK: Yeah, I guess I'm still thinking along the  
18 same line that I spoke on because I think a lot of the other --  
19 it does -- the larger study, which I think it would be good and  
20 everything, still seems more retrospective in some ways.  
21 You're going to say the incidence or whatever you've got during  
22 these things, and I'd rather, in addition or something, have a  
23 subset that really focused on this but was really looking at  
24 them, you know, as they were going and not waiting for an  
25 infarction to happen, okay, to see whether you were actually

1 getting, you know, something more happened, as you say  
2 biomarkers or whatever, noninvasive scanning or whatever you  
3 have.

4 But even if it's a smaller subset, you're kind of looking  
5 at that and trying to see if there isn't a trend or something  
6 here or if it is really a spurious result and there's nothing  
7 there.

8 DR. EDWARDS: Thank you.

9 Dr. Hoofnagle?

10 (Off microphone response.)

11 DR. EDWARDS: Okay. Dr. Ward.

12 DR. WARD: No, I think most of what's been said and, you  
13 know, the guiding principles are get the population and the  
14 surveillance at the greatest risk for this adverse event and  
15 make sure the surveillance catchment is of sufficient size to  
16 really look at the question accurately, and then monitor the  
17 data as timely as possible that we -- so that we can confirm or  
18 refute the safety concern as quickly as possible and to  
19 communicate that information as soon as possible.

20 Thank you.

21 DR. EDWARDS: Dr. Nolte, do you have a comment?

22 DR. NOLTE: I have no comment.

23 DR. EDWARDS: Thank you.

24 Yes, Dr. Packer.

25 DR. PACKER: Yeah, I just want to say that 40 to 60 is



1 actually not the age range for myocardial infarction; it's  
2 older than that and just -- if we see patients with an MI who  
3 are in their 40s and 50s, we consider that to be highly  
4 unusual. This is a disease in an older population.

5 DR. HOOFNAGLE: Could I ask a question of Dr. Packer? You  
6 mentioned that there are some instances where the MACE doesn't  
7 work, that it's a specific diagnosis, it's different than the  
8 rest. Can you give us an example of that?

9 DR. PACKER: Yes. The data originally on rosiglitazone  
10 was an MI signal only, no stroke. The original data on COX-2  
11 inhibitors was in myocardial infarction signal. There was a  
12 minor stroke signal. So you can have these imbalances. Please  
13 understand that the only reason that myocardial infarction and  
14 stroke are combined is largely because of a platelet  
15 combination as opposed to an inflammatory combination. Plaque  
16 rupture is not -- is the way that myocardial infarctions occur,  
17 but it's not the way, or the primary way, that strokes occur.

18 DR. HOOFNAGLE: But weren't both of those examples maybe  
19 not correct?

20 DR. PACKER: The COX-2 inhibitor example is unbelievably  
21 correct. That's why we only have one of them on the market.

22 DR. EDWARDS: Pam, do you want to comment on whether -- a  
23 more specific subpopulation you would be more comfortable with?

24 DR. McINNES: I'm struck by looking at the population in  
25 which Dynavax so bravely ventured, and I think it is brave.

1 It's an incredibly unhealthy group of people. When I look at,  
2 you know, the BMI, the diabetes, the cardiac disease, the drug  
3 abuse, the yada, yada, yada, yada, it just goes on and on and  
4 on, and maybe it's a miracle you didn't find more problems than  
5 this.

6 So I think this is the problem because we're used to  
7 thinking about, you know, relatively healthy, pure populations  
8 in which we introduce -- certainly in pediatrics that's what  
9 we're used to thinking about.

10 And so here you've got this conundrum, and now you've got  
11 a signal, and is it can you construct somewhat in order to  
12 launch this and get maybe additional studies to help you  
13 broaden that population? Or, in fact, does that strategically  
14 present problems in the long haul? And we have examples of a  
15 pediatric vaccine that struggled with that very same issue.  
16 Never quite had the data for the younger population, launched  
17 with an older, and probably never recovered.

18 So I would have to -- I don't think I have anything very  
19 intelligent to say about this, this afternoon. I have to think  
20 a lot more about it now that I'm no longer thinking about the  
21 whole pool. I think there are perhaps -- if you're seeking an  
22 indication for 18 and older, I don't dismiss the younger  
23 population. I think that's your indication you're seeking, and  
24 I think your signals won't be there, and I think it's a much  
25 easier way to go. Are they the population that particularly

1 need this vaccine? Probably not. So that's the yin and the  
2 yang of that one.

3 That's really where I am at this point. I am going to  
4 think more about it. I'm worried about the Asian data. When I  
5 looked at it, I thought it was regrettable that there was not a  
6 bigger body of data in Asians because of the burden of disease  
7 that is pouring in.

8 DR. EDWARDS: So in terms of the Question 3, we've sort  
9 of -- I'm not sure we need -- we've sort of addressed that.

10 DR. GRUBER: You know, we just had some sidebar  
11 conversation and e-mailed the FDA on really where to take this  
12 given the vote: 11 yes, 1 no. But we still felt, you know, we  
13 had three members that abstained. It will be great if those  
14 three members could opine, at least, on Question 3, okay? I  
15 don't think it's necessary to really turn it into a yes/no  
16 vote, but the issue about "Do the presented data support usage  
17 in a more specific subpopulation," given that these three  
18 members didn't vote yea or nay, I think it's -- I would really  
19 like to hear them elaborate on that a bit.

20 DR. EDWARDS: So Dr. Lee, Dr. Packer, and Dr. Levy could  
21 comment on that. Yes?

22 DR. BENNICK: A comment.

23 DR. EDWARDS: Jack.

24 DR. BENNINK: Pam, in terms of what you said, though, in a  
25 sense, the risk-benefit ratio is greater in that population

1 that has the most risk as well. Wouldn't you think that that's  
2 true?

3 DR. McINNES: Jack, I wish it just -- that's never how it  
4 plays out in vaccines. Okay, we don't intellectually sit there  
5 and say, oh, the benefit is this and the risk -- it's not how  
6 it happens; you get hammered. When it doesn't work out right,  
7 you get hammered. So I'm concerned. I'd say yes,  
8 intellectually that makes a lot of sense. Does it work that  
9 way? It doesn't work that way. So it concerns me.

10 DR. EDWARDS: Okay, so Dr. Lee, are there any more  
11 specific subpopulations that you would support usage in?

12 DR. LEE: From the efficacy study, it seems that this  
13 vaccine is used for, for population except the older age, so  
14 that's just my concern. Yeah, okay.

15 DR. EDWARDS: So age, the older age would be one that you  
16 would be more concerned about? Okay.

17 DR. LEE: Right.

18 DR. EDWARDS: Okay, Dr. Packer.

19 DR. PACKER: Actually, I think it would be self-defeating  
20 to restrict this to a subpopulation because if you want to do a  
21 postmarketing study and you want to get the answer, you would  
22 like to get the answer in a high-risk population, which means  
23 that the vaccine has to be available to a high-risk population.  
24 So if you really want to get an answer about myocardial  
25 infarction, you have to allow the vaccine to be used in high-

1 risk people.

2 DR. EDWARDS: Dr. Levy.

3 DR. LEVY: Yeah, I agree with Dr. Packer.

4 DR. EDWARDS: Dr. Sun, did you have a comment?

5 DR. SUN: Yeah, I just want to make a comment to  
6 Dr. Packer's points. I think when we framed this question  
7 originally, it was a measure to mitigate the risk, it's going  
8 back to risk-benefit, and we were thinking that if the signal  
9 were reopened, how we might -- might we mitigate that risk and  
10 still allow the vaccine to go forward and that was -- that's  
11 the reason why we are asking the question that is -- we had  
12 examples in vaccines where we approved an indication, age, and  
13 usage in a limited number and then extend that by further  
14 studies when the vaccine is licensed.

15 DR. PACKER: Maybe I can just quickly -- there's actually  
16 only one risk here, and that risk -- and it's a really horrible  
17 risk -- is that 3 years from now you still won't know the  
18 answer. That's the risk you don't want to take.

19 DR. LEVY: Yeah. And I want to echo that, and that's why  
20 a lot of the panelists kept harping on having an excellent  
21 postmarketing plan, because the worst outcome would be to have  
22 a muddle and we still don't know, and the public starts picking  
23 up on this and there are all sorts of concerns. So that's why  
24 having real clarity from the FDA -- and I know Marion has  
25 spoken to this, but that's why we keep coming back to this

1 point, how rigorous can it be at the postmarketing level, and  
2 are your statisticians satisfied that you'll have, within a  
3 year or a year and a half, you know, a clear answer. That's  
4 critical, right?

5 DR. EDWARDS: Dr. Lee.

6 DR. LEE: Yes. My original comment was -- I meant to say  
7 that I suggest the approval of the use of the vaccine, but with  
8 post-license studies emphasized, with emphasis on the older  
9 people because they're -- they may have higher incidence, yeah.

10 DR. EDWARDS: Okay. So the fourth question, then, is  
11 "What additional studies (either pre- or post-licensure) are  
12 needed to further evaluate the safety in the general adult  
13 population or in specific subpopulations?"

14 We've sort of beaten this horse quite mercilessly. Are  
15 there any other thoughts or comments about additional studies  
16 that we haven't commented on?

17 John.

18 DR. WARD: I don't know when certain populations like  
19 pregnant women, you know, get brought up, but it seems like  
20 there are certain populations that are always of a concern  
21 about vaccination. I know just the recommendation for the use  
22 of the current hep-B vaccinations were just -- just in the  
23 last, you know, 10 years were -- you know, there was a  
24 recommendation that you could vaccinate pregnant women. And so  
25 maybe that will be by extension you can use this one as well,

1 but that is one population that there's always a safety concern  
2 about.

3 DR. EDWARDS: So I think that there is a registry for  
4 pregnant women that is proposed, but it would not be a vaccine  
5 recommended for pregnant women.

6 Yeah, Jan.

7 DR. ENGLUND: I really think, and it was brought up in the  
8 comment period, but adolescents are a high-risk group, and it  
9 would really -- I know this is going down to 18, but if we  
10 could get a vaccine like this down to 16, that adolescent  
11 population is a high-risk vulnerable group that we have a hard  
12 time accessing, and I would really, really recommend urging  
13 that we get this for adolescents.

14 DR. LEVY: And I agree with Janet; that's a great point.  
15 And as a pediatrician, that 18 mark is, you know, kind of  
16 pulled out of a hat and, you know, has just kept -- promulgated  
17 with a lot of problems associated with it. I noticed that one  
18 of the studies presented by the Sponsor went down to age 11  
19 years; did I see that correct?

20 DR. EDWARDS: There were a few --

21 DR. LEVY: Very few, yeah.

22 DR. EDWARDS: -- that were excluded. But Dr. Lynfield and  
23 I used our combined math ability during the dinner to just  
24 remind us that the routine use of vaccine for infants has been  
25 now 26 years, so there's a lot of people, obviously not 100%,

1 but a lot of children that had been immunized.

2 DR. ENGLUND: But are immigrants and the people who move  
3 here and -- so I still think that the adolescent -- I would  
4 also suggest it would be nice, maybe, to have --

5 DR. EDWARDS: Further studies, perhaps.

6 DR. ENGLUND: -- further studies in HIV positive,  
7 especially those who may not be as well controlled, because  
8 this vaccine looks so good that you could maybe use it even if  
9 they're not well controlled at the beginning, yeah. Excluded  
10 from this, from this study, right? Yeah.

11 DR. EDWARDS: So some of those special populations that  
12 were excluded might be included, and also some studies of the  
13 people who don't respond to the routine, or even a mix-and-  
14 match to see whether one dose would do the trick, perhaps.

15 Yes, Dr. Hoofnagle.

16 DR. HOOFNAGLE: Yeah, I agree with the non-responder, and  
17 this way you can bring in the adolescents who should've gotten  
18 a hepatitis B vaccine, and if they have substandard levels  
19 below 10, use of this vaccine to boost would be nice to show  
20 the safety and efficacy in that situation. And  
21 immunosuppressed patients, not just HIV, but people on  
22 corticosteroids, bone marrow transplant recipients, liver  
23 transplant recipients.

24 And then let me bring up the issue of what hepatologists  
25 are very involved with, which is reactivation of hepatitis B,



1 and what this is, is you've recovered from hepatitis B, but it  
2 comes back; it's a DNA virus and it persists for life. So you  
3 can be completely recovered and have antibody, and if you're  
4 immunosuppressed or have a bone marrow transplant, hepatitis B  
5 comes roaring back and can be quite severe. The mortality rate  
6 is 10%. So these people are usually given hepatitis B  
7 therapies to prevent reactivation.

8 But the Japanese have shown that if you have a titer of  
9 antibody above 100, which is reachable by these vaccines, the  
10 reactivation in that situation doesn't occur.

11 So this would be a wonderful situation, kind of, to test  
12 that as opposed to a lifelong use, like a bone marrow  
13 transplant patient, lifelong use of hepatitis B viral --  
14 antiviral. So that's another niche area but an area that can  
15 give you fast and very important data. That's not so much  
16 safety as efficacy, but the safety comes in the  
17 immunosuppressed person, certainly in the transplant patients  
18 who have very high rates of coronary disease and stroke and so  
19 forth.

20 DR. EDWARDS: Thank you.

21 Any other additional study designs or --

22 DR. PORTNOY: Yeah, I would just like to -- the comment  
23 that the CpG adjuvant, the TLR9 agonist that we're talking  
24 about has been studied in allergen immunotherapy studies. I  
25 know that there were a number of studies done looking at that;

1 the abstracts weren't approved because efficacy was hard to  
2 demonstrate for a variety of reasons. But you could check with  
3 those studies and see what the safety data shows about  
4 cardiovascular events in those studies. It's something that  
5 you might want to take a look at.

6 DR. PACKER: Just a question. What was the age range in  
7 those studies?

8 DR. PORTNOY: It was -- well, I think they were adults. I  
9 don't know that they went up to, really, old adults whose -- it  
10 was allergic individuals, so most of the people in those  
11 studies would be in their 20s and 30s, but I know they included  
12 people in their 50s and 60s. I don't recall hearing, or at  
13 least I don't recall, any information about cardiovascular  
14 events in those studies. But it's something that you might  
15 want to take a look at.

16 DR. EDWARDS: Dr. Coffman.

17 DR. COFFMAN: Can we turn this on? Yeah, thank you. Bob  
18 Coffman, Dynavax.

19 I guess I'm the only survivor of the days when we had --  
20 were working on that project. We didn't really include -- deal  
21 with that so much in the safety. I actually don't know whether  
22 we saw any cardiovascular events. Certainly, the overall  
23 safety profile was reasonably pristine on all those studies.

24 But I do want to point out, although the people got  
25 multiple injections, usually six, it was in a form of a

1 conjugate with an allergen, and the actual doses were much,  
2 much lower, most about 20 or 30 µg per injection rather than  
3 3 mg. So I think it has limited value for our discussion, in  
4 any event. We'll go back and look. We didn't even actually  
5 dig up that data in terms of this filing.

6 DR. EDWARDS: Thank you.

7 DR. BENNINK: But Bob, in the -- you're doing a lot of  
8 cancer ones as well.

9 DR. COFFMAN: Yeah.

10 DR. BENNINK: I mean, are those higher doses or are those  
11 all relatively small numbers of people, too?

12 DR. COFFMAN: Still fairly small numbers of people, you  
13 know, in terms of other therapeutic programs with our cancer  
14 drugs, both cancer in a trial and hepatitis C patients. We're  
15 up to maybe 150 people there. We've not seen any signal, I  
16 don't recall a signal for MI, but I think the numbers are too  
17 small to include.

18 DR. EDWARDS: Okay. So, Dr. Gruber, are there any other  
19 questions that you would -- it looks like we have addressed  
20 them. Are there any other comments?

21 DR. GRUBER: Let me just confer with my colleagues.

22 DR. EDWARDS: Please.

23 (Pause.)

24 DR. GRUBER: We're good. We thank the Committee.

25 DR. EDWARDS: Okay. And I want to thank the Committee and

1 also the FDA and the Sponsors for the very succinct and clear  
2 presentations and for the new product.

3 CAPT HUNTER-THOMAS: Thank you, everyone. And this  
4 meeting is now adjourned.

5 (Whereupon, at 3:22 p.m., the meeting was concluded.)

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## 1 C E R T I F I C A T E

2 This is to certify that the attached proceedings in the  
3 matter of:

4 147TH MEETING OF THE VACCINES AND RELATED BIOLOGICAL PRODUCTS  
5 ADVISORY COMMITTEE

6 July 28, 2017

7 Silver Spring, Maryland

8 were held as herein appears, and that this is the original  
9 transcription thereof for the files of the Food and Drug  
10 Administration, Center for Biologics Evaluation and Research.

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Court Reporter

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