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P R O C E E D I N G S (8:30 a.m.)

Agenda Item: Call to Order and Opening Remarks

DR. DAUM: Good morning and welcome to the 131st meeting of the Vaccines and Related Biological Products Advisory Committee with the catchy acronym VRBPAC. As is our custom, we will turn the floor over to Don Jehn, our designated federal official, for some opening remarks.

MR. JEHN: Good morning, thanks Dr. Daum. Just before we read the statement of conflict of interest supplement for today, just note to all that Rita Chappell is the FDA press office back there. She is raising her hand. If anybody has any, contact her.

Agenda Item: Conflict of Interest Statement

MR. JEHN: I would like to read this COI disclosure statement. This brief announcement is in addition to the conflict of interest statement read at the beginning of the meeting on November 14, 2012, and will be part of the public record on November 15, 2012. The committee will discuss and make recommendations on the safety and efficacy of hepatitis B vaccine manufactured by Dynavax. This is a particular matter involving specific parties.

Based on the agenda and all financial interest reported by members and consultants, no waivers were issued

under 18 US Code 208. Dr. Filip Dubovsky is serving as the industry representative acting on behalf of all related industry. He is employed by MedImmune LLC. Industry representatives are not special government employees and do not vote.

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

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

FDA encourages all of their participants to advise the committee of any financial relationships that

you may have with any affected firms, the products, and if known their direct competitors. Thank you. I'll turn the meeting over to Dr. Daum.

DR. DAUM: Thank you very much. Two brief announcements. One is, anybody with electronic devises that will make noise, please either turn them off or turn them to vibrate so we don't get interrupted by them going off. The second thing is that the folks seated at the committee table to my right had an issue in previous session whereby their backs are to the sponsors, and they want to turn around and face the sponsor when they are asking a question.

But then we can't hear because they are not facing the microphone. So I am going to ask everybody on the right side of the table to be rude and to speak into the microphone. I think everyone will hear and we can turn around and face each other for the response. I apologize for that, but that is the way this room is set up.

Since the committee has a little bit of a different composition than yesterday I would like to do the requisite introductions and start with Dr. Dubovsky and go around the table.

DR. DUBOVSKY: I am Filip Dubovsky. I am serving as the industry rep. I am a peds ID guy and I head up the

clinical development of vaccines and efficiencies products at MedImmune.

DR. CHEUNG: My name is Ambrose Cheung. I came from Geiser School of Medicine at Dartmouth and I work in the molecular pathogenesis of bacteria.

DR. MURPHY: Trudy Murphy with the Centers for Disease Control, Division of Viral Hepatitis, and I am the CDC lead for the Hepatitis ACIP Working Group.

DR. BENNINK: I am Jack Bennink. I am from the NIH, from the National Institutes of Allergy and Infectious Diseases. I am in the Laboratory of Viral Diseases. I am Chief of the Viral Immunology section.

DR. PIEDRA: Pedro Piedra, at Baylor College of Medicine, Houston, Texas, Pediatric Infectious Disease, and I work on respiratory viruses.

DR. MARCUSE: Ed Marcuse, the University of Washington Schools of Medicine and Public Health. I am a pediatrician and I have had a career-long interest in vaccines and immunization.

DR. WHARTON: Melinda Wharton, Centers for Disease Control and Prevention. I am in the National Center for Immunization and Respiratory Diseases where our national immunization program resides.

DR. MCINNES: Pamela McInnes, the National

Institutes of Health.

DR. BRADY: Nate Brady, private practice allergy, immunology, and I also serve as the consumer representative.

DR. GELLIN: I am Bruce Gellin and I direct the National Vaccine Program Office at HHS.

DR. HUDGENS: Michael Hudgens from the Department of Biostatistics at the University of North Carolina.

DR. AIR: Gillian Air, University of Oklahoma Health Sciences Center.

DR. TACKET: Carol Tacket, the University of Maryland Center for Vaccine Development.

DR. GRAY: Greg Gray, University of Florida Public Health, epidemiology.

DR. SUN: Wellington Sun, Director of Division of Vaccines, CBER.

DR. GRUBER: Marion Gruber, Office of Vaccines, CBER.

DR. SMITH: Lorie Smith, Office of Vaccines, CBER.

DR. WOROBEC: Alexandra Worobec, Medical Officer, CBER, FDA, OVRR, Office of Vaccines.

DR. DAUM: And I am Robert Daum. I am a pediatrician at the University of Chicago and work on

pathogenesis of staph and mechanisms of antibiotic resistance. That is our committee, and we are ready to swing into the agenda item for today, which is the safety and efficacy of a Hepatitis B vaccine manufactured by Dynavax, and we will go right forward to our first presentation which is by Dr. Marion Major, the Acting Chief of LHV and about six other acronyms at FDA. Good morning, Dr. Major. She will introduce the topic and present the questions that we will be voting on later today.

Agenda Item: Topic 2: Safety and Efficacy of a Hepatitis B Vaccine Manufactured by Dynavax

Agenda Item: Introduction and Presentation of Questions

DR. MAJOR: Thank you very much and welcome everyone here today. I would like to extend a welcome to distinguished members of the VRBPAC panel and particularly to our subject matter experts. Thank you all very much for coming here today. Today we are going to discuss at Hepatitis B Vaccine, it is recombinant, adjuvanted. It contains Hepatitis B surface antigen with a 1018 ISS, which is a CPG adjuvant. And this vaccine will be referred to as HEPLISAV. And the applicant is Dynavax Technologies Corporation.

To give a little background on currently licensed

Hepatitis B vaccines, these are both approved for immunization against infection caused by all known subtypes of Hepatitis B virus. There is ENGERIX-B, which is manufactured by GlaxoSmithKline. It was licensed in 1989. It consists of recombinant hepatitis B surface antigen which is produced from yeast cells, and absorbed onto aluminum hydroxide.

And then there is RECOMBIVAX HB, which is manufactured by Merck. This was licensed in 1986. It is also recombinant hepatitis B surface antigen, again produced from yeast cells, and it is all onto aluminum hydroxyphosphate sulfate.

Dosage and administration of these two vaccines are both administered through the intramuscular route. For ENGERIX-B, for persons from birth through 19 years of age receive three doses containing 10 micrograms each of recombinant hepatitis B surface antigen, given at zero, one and six months.

Persons 20 years of age and older receive three doses containing 20 micrograms of surface antigen, at zero, one and six months. And adults on hemodialysis received a series of four doses, 40 micrograms each of surface antigen, given at zero, one, two, and six months.

For RECOMBIVAX, very similar. Persons from birth

through 19 years of age receive three doses, each containing five micrograms of surface antigen, given on a zero, one, and six month schedule. Persons 20 years of age and older receive three doses, 10 micrograms of surface antigen each, zero, one, and six months. And adults on hemodialysis receive three doses, each containing 40 micrograms of surface antigen given on a zero, one and six month schedule.

There are also a number of currently licensed combination hepatitis B vaccines. The hepatitis B component in all of these vaccines is the same of that previously described for the monovalent vaccines ENGERIX or RECOMBIVAX.

From GlaxoSmithKline there is TWINRIX, which is indicative immunization against hepatitis B and hepatitis A for persons 18 and older, PEDIARIX for immunization against diphtheria, tetanus, pertussis, hepatitis B and polio. And this is for children six weeks through six years. And from Merck there is COMVAX for immunization against haemophilus influenza type b and hepatitis B. And this is for infants six weeks to 15 months.

There are some alternate dosing schedules for these licensed vaccines. For ENGERIX-B, for infants born to carrier mothers and children from birth through 10 years

of age, can receive four doses, each containing 10 micrograms of surface antigen, given at zero, one, two months, with a boost at 12 months.

Children five through 10 years of age and adolescents 11 through 16 can receive three doses, 10 micrograms each, of surface antigen given on a zero, 12 and 24 month schedule. Adolescents 11 through 19 receive three doses, 20 micrograms of surface antigen, given on zero, one and six month schedule. And adolescents 11 through 19 and adults 20 years of age and older can receive four doses, each containing 20 micrograms of surface antigen, given at zero, one and two months with a boost at 12 months.

TWINRIX has an accelerated schedule for individuals 18 years of age and older. They can receive four doses. These are given at zero, seven and 21 to 30 days, and then a boost at 12 months. And for RECOMBIVAX, adolescents from 11 through 15 receive two doses, 10 micrograms each, of hepatitis B surface antigen given at zero time point and four to six months later.

So moving to HEPLISAV, the composition, a proposed indication and the dosage, HEPLISAV also consists of recombinant hepatitis B surface antigen produced from yeast cells. This is combined with a 1018 ISS adjuvant, which is a cytosine phosphoguanosine oligodeoxynucleotide.

And you will see this referred to as CpG-ODN.

CpG-ODNs are not contained in any currently licensed US vaccines. HEPLISAV, the proposed indication is for immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 through 70 years of age. And the dosage is two doses, each containing 20 micrograms of recombinant surface antigen with 3,000 micrograms of the 1018 ISS adjuvant, given on a zero and one-month schedule.

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

Just to give a very general definition of the difference between Th1 and Th2 responses, Th1 responses generally speaking are characterized by the production of proinflammatory cytokines, such as interferon gamma and TNF alpha, which leads to a cell mediated immunity, and also an

opsonizing antibody response, which is characterized by an IgG2a isotype.

Th1 responses are characterized by interleukin-4 production, in addition to a number of other cytokines. And this leads to a solely humoral immune response which is dominated by IgG1 and IgE antibodies.

So the CpG mode of action -- CpGs are classed as toll-like receptor, or TLR agonists. TLRs are proteins on innate or first responder immune cells, such as monocytes and dendritic cells, and these recognize molecules from invading microbes.

TLRs recognize molecules shared by many different microbes, but these molecules are distinguishable from host molecules. CpGs function via TLR-9, and TLR9 is expressed mainly on plasmacytoid dendritic cells and memory B cells. The proposed mechanism of action for 1018 ISS is that it stimulates TLR9 in plasmacytoid dendritic cells that have taken up recombinant hepatitis B surface antigen.

This converts the dendritic cells into activated dendritic cells, that then present hepatitis B surface antigen epitopes to the immune system. This promotes differentiation of CD4 positive cells, that leads to antibody secretion by hepatitis B surface antigen specific B cells.

Now I would like to talk a little bit about the use of anti hepatitis B surface antigen antibody to predict protection. Early hepatitis B vaccine trials use the prevention of HBV infection as the clinical endpoint. And data from these early vaccine studies which actually used Heptavax, which was a plasma-derived hepatitis B surface antigen vaccine, this was surface antigen derived from plasma from patients.

These studies showed that anti-HBs antibody levels of greater than 10 milli-IU per ml correlated with protection. And now, post vaccination, an anti-HBs level greater than or equal to 10 milli-IU per ml is accepted as conferring protection. And this type of correlate of protection can be used as an indicator of clinical effectiveness in a traditional route for licensure.

So what of the information regarding levels of anti-HBs and protection? Now it is understood and known that initial anti-HBs levels have been associated with greater persistence of the antibody in vaccinees. However, in considering long-term protection, this is not really relevant. Decreased titers to less than 10 milli-IU per ml, or even complete disappearance of anti-HBs does not necessarily mean a loss of protection.

Immunological memory is maintained in vaccinees

despite declines in anti-HBs levels. And although anti-HBs may become undetectable in a substantial proportion of vaccine responders, breakthrough infections are rare and mainly asymptomatic.

In terms of the duration of protection, data from prolonged follow up studies using the plasma-derived hepatitis B vaccine have shown that an estimated 92.5 percent of primary responders had evidence of continued protection after 22 years, and no vaccine recipients became chronically infected.

Now the data for the recombinant hepatitis B surface antigen vaccines does not go out as long as 20 years. But so far these vaccines have been shown to confer long-term protection and persistent immunological memory for at least 10 years.

So moving on to the HEPLISAV clinical studies, seroprotection rate, or SPR, was used as the endpoint to support effectiveness. And SPR is defined as the proportion of individuals achieving an anti-HBs concentration of greater than or equal to 10 milli-IU per ml after vaccination. You are going to hear today about two pivotal Phase 3 trials, DV2-HV-10 and DV2-HBV-16. And then in these studies Dynavax compared immune responses following injection with either two doses of HEPLISAV or

three doses of ENGERIX-B.

So the questions to the committee today -- one, are the immunogenicity data adequate to support the effectiveness of HEPLISAV for the prevention of hepatitis B virus infection in adults 18 through 70 years of age? Please vote yes or no. And two, are the available data adequate to support the safety of HEPLISAV when administered to adults 18 through 70 years of age? Please vote yes or no.

If yes, is the proposed pharmacovigilance plan adequate to further evaluate the safety of HEPLISAV post-licensure? If no, please discuss what additional studies, pre- and post-licensure, are needed to further evaluate the safety of HEPLISAV. Thank you.

DR. DAUM: Thank you very much, Dr. Major. Committee members may now question Dr. Major with regard to clarity of presentation. We will have time to come back to any heavy duty issues this afternoon.

DR. CHEUNG: On the antibody response, are you suggesting that IgG2a are more opsonic than IgG1? I thought there are tons of antibodies that are opsonic that belong to IgG1.

DR. MAJOR: I’m sorry, did you say is it suggesting IgG2a isotype is more opsonizing than IgG1?

DR. CHEUNG: Yes.

DR. MAJOR: Generally I think that is accepted that they are. But I think it is a very broad definition, so it doesn’t mean that IgG1 cannot.

DR. PIEDRA: Just for clarification, and I think it is along the same lines, I think that is more for mouse data rather than for human data.

DR. DAUM: What do you mean by it?

DR. PIEDRA: The IgG2a as better opsonization, I think that is more in reference for a mouse rather than for humans. And so I am not sure --

DR. MAJOR: Yes, I think that was a very broad definition of the two, so I think that it is not necessarily saying that it does not, IgG1 is not opsonizing, or IgG2a is the sole opsonizing antibodies. But I think that is just the general way that these two terms are defined.

DR. DAUM: Dr. Murphy?

DR. MURPHY: Yes, just for clarification on slide 14, the long term protection studies from Dr. McMahon, I believe those studies eliminated people who are non-responders. Is that correct?

DR. MAJOR: Yes. So these are just vaccine recipients that responded and received the full course of

the vaccine.

DR. DAUM: Other clarifying questions? (none) Okay, we thank you, Dr. Major. We are running a few minutes ahead of schedule on an airplane day, which is good. And we are now going to see a feat of amazing agility, which is the sponsor has got five speakers and one hour. So I leave it to them to try and do that and introduce Dr. Martin, who is the first speaker from the sponsor. You actually have an hour and seven minutes if you need it.

Agenda Item: Sponsor Presentation

DR. MARTIN: Thank you. Adult hepatitis B infection is a serious public health issue. Dynavax is pleased to be here today to work with this committee to further advance adult immunization against hepatitis B by turning theoretical concepts into real options for protection against this highly infectious virus which continues to cause substantial morbidity and mortality.

Mr. Chairman, members of the Committee, ladies and gentlemen, I am Dr. Tyler Martin, Chief Medical Officer at Dynavax technologies. HEPLISAV is an innovative vaccine that uses a new adjuvant to surmount the limitations of current hepatitis B vaccines. The new adjuvant is 1018 ISS, a toll-like receptor 9 agonist that activates the

innate immune system, preparing the adaptive immune system for an enhanced response.

This vaccine represents an opportunity to substantially improve our ability to protect adults in the United States at risk of hepatitis B infection. HEPLISAV combines yeast derived recombinant hepatitis B surface antigen with 1018 ISS, which replaces the alum adjuvant in current vaccines. The surface antigen in HEPLISAV is manufactured in Hansenula polymorpha, and is very similar to the antigen in licensed hepatitis B vaccines.

1018 ISS is a synthetic phosphorothioate oligonucleotide. HEPLISAV is a sterile liquid dosage form. Each dose contains 20 micrograms of surface antigen, and 3,000 micrograms of 1018 ISS adjuvant. The dosing regimen is two 0.5 mill doses, administered one month apart. The HEPLISAV clinical development program started in 2000 and led to the finding of this BLA for the prevention of hepatitis B infection in adults 18 to 70 years of age.

It includes two pivotal trials and six supportive trials involving 5,845 subjects. Five additional trials have been conducted in subjects with chronic kidney disease and will be included in a supplemental application. The goal of hepatitis B vaccines is to induce antibodies to the hepatitis B surface antigen or HBS.

Results from early efficacy trials of hepatitis B vaccines showed that an anti HBS concentration of 10 milli-International Units per mill or greater after vaccination correlates with long term protection against hepatitis B.

Individuals who never achieve an anti HBS concentration of 10 or greater following vaccination remain susceptible to hepatitis B infection. On a population level the immunogenicity of hepatitis B vaccines is typically expressed in terms of the seroprotection rate or SPR. The SPR is the proportion of individuals achieving an anti HBS concentration of 10 or greater after vaccination. A lower SPR indicates that more vaccinees remain susceptible to infection.

The HEPLISAV clinical development program used SPR as the primary endpoint variable in all trials. After this introduction, Dr. William Schaffner, professor and Chair of the Department of Preventive Medicine at Vanderbilt Medical School will describe the need for an improved hepatitis B vaccine for adults in the United States.

Dr. Greg Poland, professor of Medicine and Infectious Diseases and Director of the Vaccine Research Group at the Mayo Clinic, will explain the scientific rationale for HEPLISAV. Dr. Robert Jansen of Dynavax will

then discuss the greater immunogenicity of HEPLISAV. And I will then demonstrate that the immunogenicity benefit is achieved without compromising safety.

Dr. Poland will return to present the favorable risk benefit profile of HEPLISAV, and I will return to conclude. Now I would like to introduce Dr. Schaffner.

DR. SCHAFFNER: Thank you. Good morning, everyone. I am Dr. William Schaffner. I chair the Department of Preventive Medicine at Vanderbilt Medical School and I am the past president of the National Foundation for Infectious Diseases and I am a liaison representative to the Advisory Committee on immunization practices. I have received consulting honoraria for my time. I do not have any financial interest in the company or the outcome of this meeting.

Safe and effective vaccines against hepatitis B infection have been available in the United States since 1981. The Advisory Committee on Immunization Practices has recommended them for use in adults with risk factors for hepatitis B infection since 1982. Those at higher risk for infection include, first, persons with potential sexual exposure, such as persons with multiple sex partners, men who have sex with men, and all persons with a sexually transmitted disease.

Second, persons with potential percutaneous or mucosal exposure, such as injection drug users, patients with chronic kidney disease, health care workers, and others who could be exposed to blood or body fluids at work. And recently recognized, persons with diabetes who may be exposed by shared blood glucose monitoring equipment.

Vaccinating at risk adults before they become infected is very challenging due to lack of access, compounded by the need to deliver three doses over six months as most persons do not develop serum protection until after the third dose. In response to these challenges of vaccinating at risk adults, in 1991 the ACIP recommended universal hepatitis B vaccination for infants, catch up vaccination of previously unvaccinated children and adolescents and ongoing vaccination of at risk adults. These strategies have decreased the incidents of new hepatitis B infections.

Hepatitis B incidence is now lowest in persons under 20 years of age, and highest in persons in their thirties, forties and fifties. Today, 84 percent of new hepatitis B infections occur in adults over the age of 30. The incidence of acute hepatitis B infections in older adults has declined much less than in those younger than

30, in part due to differences in vaccination coverage by age.

While persons up to 20 years of age are largely immunized, there remains a substantial cohort of unimmunized adults who are at continuing risk of hepatitis B infection. Hepatitis B infection therefore remains a major health problem among adults living in the United States.

The Centers for Disease Control and Prevention estimates that there were 38,000 new infections and 3,000 deaths from hepatitis B related complications in 2010. The groups with the highest incidence of acute infection include men 30 to 45 years of age, persons with diabetes and persons of black race.

Up to 2.2 million persons in the United States are living with chronic hepatitis B infection. Recently the impact of hepatitis B infection on persons living with diabetes has been recognized as a major public health issue. CDC estimates that 4,000 cases of hepatitis B infection occur annually in persons with diabetes, accounting for more than 10 percent of all new infections in the United States.

Acute hepatitis B infections in persons with diabetes has a case fatality rate as high as 18 percent,

and chronic infection rates as high as 45 percent. Both of these rates are much higher than in the general population. In October 2011 these findings led the ACIP to recommend hepatitis B vaccination for adults with diabetes.

The challenge of vaccinating adults against the hepatitis B virus is multifactorial. Access to persons at risk for infection and vaccine coverage remain important challenges both to health care providers and to public health authorities. In addition, there are limitations to the current vaccines. These vaccines are less immunogenic in adults, generating lower rates of seroprotection than in children and adolescents.

Many people find it difficult to complete the entire three dose regimen. In addition, since the third dose is required for seroprotection in most adults it delays time to seroprotection. The immunogenicity of current hepatitis B vaccines peaks in adolescence and then begins to decline with age. Seroprotection rates decline to less than 90 percent in persons over the age of 40, and are less than 75 percent in persons over the age of 60.

In addition to this general immunosenescence, specific adult subpopulations are hyporesponsive to current hepatitis B vaccines, that is, current vaccines induce lower rates of seroprotection in these subpopulations,

resulting in a higher proportion of individuals who remain susceptible to hepatitis B infection despite having been vaccinated. Men, obese persons, persons who smoke, and persons with diabetes are all such hyporesponsive subpopulations.

There is a public health need to effectively vaccinate these hyporesponsive subpopulations because in many cases the sequelae of hepatitis B infection are worse in these individuals. For example, in adults 40 and older the mortality rate of acute symptomatic infection is higher than in 18 to 39 year olds. In addition, infected men experience higher rates of cirrhosis and hepatocellular carcinoma than do infected women.

A significant additional challenge in protecting adults against hepatitis B is the completion of the three dose, six month schedule. In a large retrospective vaccine safety data link, VSD study of over 88,000 adults who initiated hepatitis B vaccination in medical care organizations and who were followed for eight years, 81 percent of those who initiated vaccination received a second dose. But only 64 percent completed the three-dose series within eight years.

Young adults 18 to 29 years of age had the lowest adherence rate. Only 53 percent received all three doses.

Since the complete three-dose series is required for reliable seroprotection, it is easy to see how the dosing regimen for current vaccines can limit the effective immunization of populations against hepatitis B.

An improved vaccine could provide higher seroprotection rates, particularly in populations that are hyporesponsive to current vaccines. Reducing the burden of vaccine administration through a reduced number of doses or shorter administration time could enable higher adherence with full vaccination. The excellent safety profile of current hepatitis B vaccines should of course be maintained. There is a clear need for a vaccine to improve protection against HBV infection and its sequelae among high risk adults.

Dr. Greg Poland will now describe the scientific rationale for HEPLISAV.

DR. POLAND: Good morning everybody. My name is Greg Poland and I am professor of Medicine and Infectious Diseases and Director of the Vaccine Research Group at the Mayo Clinic. I too have received consulting honoraria for my time but I do not have any financial interest in the company or the outcome of this meeting. I was the Chair of the Safety Evaluation and Adjudication Committee, or SEAC, for Dynavax’s Trial 16.

Antibody to the surface antigen of hepatitis B virus is associated with resolution of infection and protection against subsequent infection. While anti HBS is protective, recombinant hepatitis B surface antigen alone is not sufficiently immunogenic to reliably induce seroprotection. Current hepatitis B vaccines combine recombinant hepatitis B surface antigen with alum as an adjuvant and have been shown to be safe and effective inducers of seroprotection.

It is very likely that many vaccines of the future will require agonists of the innate immune system and that CPG adjuvants that stimulate TLR9 are among the most promising. The TLR4 adjuvant in Cervarix broke the ice for the use of innate immune system agonists as adjuvants, whereas the live virus vaccine stimulates strong innate immune responses, sub unit vaccines like hepatitis B vaccines, do not.

And in order to make highly immunogenic vaccines we are going to need adjuvants that enhance adaptive responses by targeting pattern recognition receptors such as TLR9. A TLR9 agonist could induce seroprotection in a higher proportion of vaccinees in a shorter time, and with fewer doses.

The first immunologic encounter between a

pathogen and a naïve host occurs via the innate immune system. Pattern recognition receptors are expressed on multiple cell types of the innate immune system, including, as you have heard, plasmacytoid dendritic cells, or I will refer to them as PDCs.

These receptors engage macro molecular components of the bacterial and viral pathogens. PDCs present processed antigen to CD4 cells, which then provide help to antigen-specific B cells. PDCs also produce cytokines that further stimulate antigen specific T and B cells.

In a protective humoral response, this combination of foreign antigens, helper T cells and cytokines causes antigen specific B cells to proliferate, differentiate into plasma cells and produce high levels of antibody against the invading pathogen. Pattern recognition receptors are divided into families based on their structures and the various patterns that they recognize. Toll like receptors are a key family of pattern recognition receptors.

There have been 10 TLRs identified in humans to date. All share structural similarities with one another, with their homologues and other mammalian species, and with the toll protein and drosophila. TLR4 is expressed on the plasma membrane and is the receptor targeted by the MPL

component of the ASO4 adjuvant system used in Cervarix, the human papilloma virus vaccine approved by the FDA in 2009.

A sub-family of TLRs located on the endosomal membrane rather than the plasma membrane recognizes foreign nucleic acids from bacteria and viruses. TLR9 recognizes DNA with unmethylated cytocine-phosphoguananine or CpG motifs. These CpG motifs are much more frequent in bacterial and viral DNA than in mammalian DNA.

In humans, TLR9 is expressed primarily on PDCs. The effects of TLR9 simulation in PDCs can be mimicked using an immunostimulatory sequence or ISS that contains optimized CPG motifs. An ISS can be tailored to elicit specific effects from PDCs. 1018 ISS has the primary effect of enhancing antigen presentation by PDCs. In animal models, 1018 ISS has been shown to enhance antibody and T cell responses by specific stimulation of TLR9.

1018 ISS has a secondary effect of rapid and transient induction of interferon alpha. When administered with hepatitis B surface antigen as the adjuvant to HEPLISAV, 1018 ISS is thought to have the following effects at the injection site and draining lymph nodes.

Stimulation of TLR9 in those PDCs that take up hepatitis B surface antigen, induction of PDCs to present surface antigen epitopes to CD4 positive T cells,

production, as I mentioned, of interferon alpha, which produces additional stimulation to surface antigen specific T cells and B cells.

This process results in a high and sustained T cell development anti-HBS response. As an adjuvant, 1018 ISS links the innate and adaptive immune systems. The immune response to HEPLISAV mimics the component of the naturally occurring immune response to viral and bacterial pathogens and live attenuated viral and bacterial vaccines. The response to stimulation of TLR9 by 1018 ISS is similar to, and more targeted than, the response to stimulation of multiple TLRs by current live attenuated vaccines.

1018 ISS is one of the new generation of targeted adjuvants that can improve immunogenicity by triggering a focused, natural immune response to selective antigens. Dr. Robert Janssen of Dynavax will now present the immunogenicity results for HEPLISAV, which uses 1018 ISS to target TLR9.

DR. JANSSEN: Good morning. I am Dr. Robert Janssen, Senior Director of Clinical Development at Dynavax Technologies. The immunogenicity of HEPLISAV compared to ENGERIX-B was demonstrated in two pivotal Phase 3 trials designated HBV 10 and HBV 16. The results demonstrate that HEPLISAV induced SPRs that were non inferior at the primary

endpoint, higher peak SPRs and higher peak SPRs in sub populations including hyporesponsive subpopulations.

Trials 10 and 16 shared key design features. Both trials were observer blind, randomized, active control and multi centered. Generally healthy adults who did not have clinically debilitating diseases were enrolled. Trial participants could not have evidence of current or past hepatitis B infection and couldn’t have received a hepatitis B vaccine prior to enrollment in the trial.

ENGERIX-B was selected as the comparator because in each of the countries where the trials were conducted it had been approved by regulatory authorities and was the most frequently used monovalent hepatitis B vaccine in adults. ENGERIX-B was administered at zero, four and 24 weeks. HEPLISAV was administered at zero and four weeks, with placebo at 24 weeks.

Concentrations of anti HBS were measured by a validated commercial assay. The first pivotal trial conducted was trial 10. Trial 10 was conducted at 21 sites in Canada and in Germany and enrolled adults 18 to 55 years of age. 2,415 adults were randomized in a three to one ratio to receive either HEPLISAV or ENGERIX-B, and they were followed for 28 weeks following the first study injection.

The second pivotal trial was trial 16. Trial 16 was conducted at 32 sites in the United States and Canada and enrolled subjects 40 to 70 years of age. 2,452 adults were randomized in a four to one ratio to receive either HEPLISAV or ENGERIX-B and were followed for 52 weeks following the first study injection.

The primary objectives in trials 10 and 16 were based on a non-inferiority design. The primary objective of both trials was to demonstrate the non-inferiority of the HEPLISAV SPR to the ENGERIX-B SPR at the primary endpoint. The protocol population was used for evaluation of the primary objective.

HEPLISAV was to be considered non-inferior to ENGERIX-B if the lower limit of the 95 percent confidence interval of the difference in SPRs, HEPLISAV minus ENGERIX-B, was greater than the non-inferiority margin of 10 percent. In both trials the proportions of subjects who completed the trial was similar in each vaccine group.

In Trial 10, 99 percent of subjects received both active doses of HEPLISAV and 97 percent received all three doses of ENGERIX-B. In Trial 16, 98 percent of subjects received both doses of HEPLISAV, and 94 percent received three doses of ENGERIX-B. The demographic in baseline characteristics most likely to affect immunogenicity were

well balanced between HEPLISAV and ENGERIX-B, and not expected to bias the immunogenicity results.

Trial 10 enrolled participants 18 to 55 years of age with a mean age of 40 years. Trial 16 enrolled participants 40 to 70 years of age, with a mean age of 54 years. In Trial 10 the primary endpoint for HEPLISAV was the SPR at week 12, which is eight weeks after the second and last active dose of vaccine.

Week 12 was chosen to reflect high levels of seroprotection in early seroprotection. The primary endpoint for ENGERIX-B was week 28 because historically the peak SPR for ENGERIX-B occurs four weeks after the last dose of vaccine.

As in Trial 10, in Trial 16 the primary endpoint for HEPLISAV was the SPR at week 12. The primary endpoint for ENGERIX-B was the SPR at week 32, eight weeks after the last dose of vaccine. Week 32 was chosen for ENGERIX-B instead of week 28 to match the time after the last vaccine dose in both groups.

In both trials, HEPLISAV met the criterion for the primary study objective of non-inferiority. In Trial 10 the SPR at the primary endpoint for HEPLISAV was 95 percent, and for ENGERIX-B 81 percent. The difference between SPRs was 14 percent, and the lower bound of the 95

percent confidence interval of the difference in SPRs was 11 percent.

In Trial 16 the SPR at the primary endpoint was 90 percent for HEPLISAV and 70.5 percent for ENGERIX-B. The difference between SPRs was 20 percent, and the lower bound of the 95 percent confidence interval of the difference in SPRs was 15 percent. Because healthy individuals who develop anti-HBS concentrations of 10 or greater after vaccination develop long term protection, a good indicator of the clinical efficacy of a hepatitis B vaccine in healthy adults is the peak SPR.

While the primary endpoint for HEPLISAV in both trials was at week 12, the peak SPR actually didn’t occur until week 24. For ENGERIX-B the peak SPR occurred at week 28 in both trials. The peak SPR in the HEPLISAV group was higher than the peak SPR in the ENGERIX-B group in both trials. In Trial 10, the peak SPR was 98 percent for HEPLISAV, compared with 81 percent for ENGERIX-B. In Trial 16 the peak SPR for HEPLISAV was 95 percent, and for ENGERIX-B 73 percent.

For analyses of subpopulations, the modified intent to treat population of Trial 10 and Trial 16 were pooled, because the larger sample size of that pooled population provides the best opportunity to explore

immunogenicity results in subpopulations of subjects. The peak SPRs in all subpopulations were higher in those who received HEPLISAV than in those who received ENGERIX-B.

Each comparison of the difference in SPRs between HEPLISAV and ENGERIX-B favors HEPLISAV, with a lower limit of the 95 percent confidence interval of the different in SPRs being greater than zero. In each subpopulation the SPR in the HEPLISAV group was 95 percent or more, except in persons with diabetes where the SPR was 89 percent.

In the ENGERIX-B group, there was variability in the SPR in hypo-responsive populations, like men, obese persons and smokers, compared with women, non-obese persons and non-smokers respectively. Of note, the highest SPR in an ENGERIX-B group was 89 percent in young adults, which was similar to the lowest SPR in a HEPLISAV group, which was 89 percent in persons with diabetes.

The consistent SPRs for the HEPLISAV group combined with the variable SPRs for the ENGERIX-B group led to variable differences in SPRs, with the lowest in young adults and the highest in persons with diabetes. In light of the recent ACIP recommendations for hepatitis B vaccination of persons with diabetes, the peak SPR in subjects with type 2 diabetes was analyzed.

The peak SPR in 222 subjects with diabetes who

received HEPLISAV was 89 percent, and in 55 subjects with diabetes who received ENGERIX-B was 62 percent. The difference in SPRs was 27.5 percent. In addition, HEPLISAV demonstrated higher peak SPRs than ENGERIX-B in all age subgroups analyzed.

In subjects 18 to 29 years of age the peak SPR was 99.7 percent for HEPLISAV compared with 92.7 percent for ENGERIX-B. One of 306 subjects less than 30 years of age who received HEPLISAV did not develop seroprotection, compared with seven of 96 subjects under the age of 30 who received ENGERIX-B who did not develop seroprotection.

In subjects 60 to 70 years of age, the age subgroup with the lowest SPRs in both vaccine groups, the SPR for HEPLISAV was 91.6 percent and for ENGERIX-B, 67.7 percent. The SPR in 60 to 70 year olds who received HEPLISAV was similar to the SPR in 18 to 29 year olds who received ENGERIX-B.

Compared with a three-dose series of ENGERIX-B given over six months, a two-dose series of HEPLISAV given over one month demonstrated higher SPRs in all analyses. HEPLISAV demonstrated non-inferiority at the primary endpoint in both pivotal trials. HEPLISAV demonstrated higher peak SPRs in both pivotal trials, and HEPLISAV demonstrated higher peak SPRs in every subpopulation

including hypo-responsive subpopulations.

Dr. Martin will now return to discuss safety. Thank you.

DR. MARTIN: HEPLISAV demonstrated a tolerability and safety profile similar to the comparative vaccine, ENGERIX-B, which is considered one of the safest vaccines in use today. The HEPLISAV clinical development program included all standard vaccine safety assessments.

And because HEPLISAV contains the 1018 ISS adjuvant, additional assessments and analysis of autoimmune events were performed throughout the development program in light of theoretical concerns regarding the safety of immune activation by adjuvants.

The safety population from all trials presented in the HEPLISAV BLA included a total of 5,845 subjects. 4,425 who received HEPLISAV and 1,420 who received ENGERIX-B. The Phase 3 safety population representing Trials 10 and 16 included a total of 4,864 subjects, 3,777 who received HEPLISAV and 1,087 who received ENGERIX-B.

The large majority of subjects in both Phase 3 trials received the full protocol specified regimen including 98 percent of subjects in the two-dose HEPLISAV group and 96 percent of subjects in the three-dose ENGERIX-B group. 95.4 percent of the HEPLISAV group and 96 percent

of the ENGERIX-B group completed the full safety follow up period.

Standard vaccine safety assessments will be presented for the Phase 3 safety population. Assessments of pregnancies and autoimmune events will also be presented for the all trials safety population. The duration of collection periods for safety events were similar between Trials 10 and 16.

In Trial 10, post-injection reactions were solicited for seven days after each injection. Adverse events and serious adverse events were collected for the entire study period of 28 weeks, which translates to 24 weeks after the last HEPLISAV injection and four weeks after the last ENGERIX-B injection.

In Trial 16, post-injection reactions were solicited for seven days after each injection. Adverse events were collected for 28 weeks. Serious adverse events were collected for the entire study period of 52 weeks, which translates to 48 weeks after the last HEPLISAV injection and 28 weeks after the last ENGERIX-B injection.

Overall, the tolerability of HEPLISAV was similar to ENGERIX-B. The rates of post-injection reactions were similar between vaccine groups, 55 percent for HEPLISAV and 57 percent for ENGERIX-B. Most injection reactions were

mild to moderate. Local post-injection reactions occurred at similar rates in both vaccine groups. Local reactions were reported by 43 percent for HEPLISAV and 41 percent for ENGERIX-B.

The most common local reaction in both groups was injection site pain, reported by 42 percent for HEPLISAV and 40.5 percent for ENGERIX-B. Most injection site pain was mild to moderate. Systemic post-injection reactions also occurred at similar rates in both vaccine groups. Systemic reactions were reported by 32 percent for HEPLISAV and 37 percent for ENGERIX-B.

The most frequent systemic reaction was fatigue for HEPLISAV and headache for ENGERIX-B. Of particular interest, fever was reported in 1.7 percent for HEPLISAV and 3.4 percent for ENGERIX-B. Adverse events were similar between vaccine groups. Adverse events were reported by 55 percent for HEPLISAV and 58 percent for ENGERIX-B. The large majority of adverse events in both groups were mild or moderate in severity.

Adverse events were also similar between groups when examined by specific adverse event. The three most frequently reported adverse events in each treatment group were the same -- nasal pharyngitis, headache, and back pain. The 10 most frequent adverse events occurred at

similar rates between groups. Syncope, a known reaction to injection, was an uncommon event, reported by 0.1 percent of subjects in both groups.

Serious adverse events were also similar between groups. 2.8 percent of the HEPLISAV group and 3.3 percent of the ENGERIX-B group experienced a serious adverse event. The relative risk of a serious adverse event in the HEPLISAV compared to the ENGERIX-B group was 0.83, with an upper bound of the 95 percent confidence interval of 1.21.

The vast majority of all serious adverse events were unrelated to vaccination. In each vaccine group one serious adverse event that was considered by the investigator to be related to vaccination occurred. Wegener’s Granulomatosis or granulomatosis with polyangiitis in the HEPLISAV group occurred 41 days after placebo injection and 172 days after the second injection of HEPLISAV.

Bronchial hyper-reactivity in the ENGERIX-B group occurred 42 days after the second injection of ENGERIX-B. Two deaths occurred in the HEPLISAV clinical program, one in each vaccine group. Both deaths occurred in Trial 16, one due to pulmonary embolism in the HEPLISAV group 46 days after the second injection with HEPLISAV, and one due to myocardial infarction in the ENGERIX-B group 47 days after

the second injection with ENGERIX-B.

Both deaths were considered by the investigators to be not related to vaccination. Limited data are available on pregnancy outcomes in HEPLISAV recipients. A total of 19 pregnancies were reported during the HEPLISAV clinical program, 14 in HEPLISAV recipients and five in ENGERIX-B recipients.

One pregnancy outcome, stillbirth at 23 weeks in the HEPLISAV group, occurred in a 29 year old woman, and the attending physician attributed the event to worsening of pre-existing chronic maternal hypertension.

This point marks the conclusion of the presentation of standard vaccine safety assessments. There is a theoretical risk that vaccines containing adjuvants may cause an increase in immune-mediated adverse reactions. These reactions could potentially include safety findings associated with auto-immune disease.

Following the occurrence of two cases of ANCA associated vasculitis in Trial 10, additional assessments for autoimmune events were performed, and following the review of these assessments with the FDA clinical development was resumed with additional monitoring procedures in place for Trial 16.

There is no known association between the anti-

HBS response and any particular autoimmune disease. Likewise, there is no evidence for a unique role for TLR9 stimulation in the initiation of any specific autoimmune disease. Therefore, in the absence of a more specific autoimmune safety hypothesis, assessments were designed to identify evidence of any autoimmune disease rather than one specific autoimmune disease.

Three assessments were used. The first was adverse events of special interest. This involved the identification, categorization and analysis of adverse events in the safety database. It was performed using a list of autoimmune and inflammatory conditions. The system was used for all trials in the HEPLISAV clinical program including the Phase 3 trials.

The second was adjudicated autoimmune events. To intensify the evaluation of autoimmune events, enhanced surveillance and identification of potential autoimmune events was performed, followed by independent adjudication by the safety evaluation and adjudication committee. This system was used only in Trial 16.

The third was laboratory assessment of auto antibodies. As potential sentinel safety biomarkers assessments of ANA and anti double stranded DNA were performed pre and post vaccination in most trials,

including Trials 10 and 16. In addition, assessments for ANCA were performed as part of the ANCA associated vasculitis investigation in Trial 10 and available supportive trials.

The list of autoimmune and inflammatory conditions used for identification of adverse events of special interest was comprehensive. This list included autoimmune and inflammatory conditions across organ systems, including neuroinflammatory, musculoskeletal, gastrointestinal, metabolic, skin, as well as other disorders affecting multiple systems.

Notably, the others category includes ANCA associated vasculitides including both granulomatosis with polyangiitis and microscopic polyangiitis. In trial 10, which used a three to one randomization ratio, nine subjects reported adverse events of special interest, five in the HEPLISAV group and four in the ENGERIX-B group.

The five subjects in the HEPLISAV group had five events: Basedow’s disease, systemic lupus erythematosus, Guillain-Barré Syndrome, granulomatosis with polyangiitis, and rheumatoid arthritis. The event of Guillain-Barré Syndrome occurred five days after influenza vaccination and 110 days after the second dose of HEPLISAV. The event was considered serious and considered by the investigator to be

not related to study vaccine.

The event of granulomatosis with polyangiitis was also serious, occurred 41 days after placebo injection and 172 days after the second dose of HEPLISAV, and was considered by the investigator to be possibly related to study vaccine.

The four subjects in the ENGERIX-B group experienced a total of six events. One subject had p-ANCA positive vasculitis or microscope polyangiitis, in addition to scleroderma and mixed connective tissue disease. Three other subjects had seventh nerve paralysis, Basedow’s Disease and Raynaud’s Phenomena.

The event of MPA was serious, occurred 126 days after the second vaccination, and was considered by the investigator to be not related to study vaccine. In Trial 16, which used a four to one randomization ratio, three subjects reported adverse events of special interest. All three subjects were in the HEPLISAV group.

The three events in the HEPLISAV group were: erythema nodosum, seventh nerve paralysis and vitiligo. All events were non-serious and mild or moderate in severity. Erythema nodosum was considered possibly related to vaccine by the investigator. Seventh nerve paralysis was considered not related. Vitiligo was considered

possibly related.

In the supportive trials, in the HEPLISAV clinical program, which represents the addition of 648 HEPLISAV recipients and 333 ENGERIX-B recipients, adverse events of special interests were identified in two HEPLISAV recipients and one ENGERIX-B recipient. In the HEPLISAV group there was one event of seventh nerve paralysis and one event of rheumatoid arthritis. The event of seventh nerve paralysis was considered serious by the investigator but did not require hospitalization.

It was moderate in severity and considered to be unlikely related to vaccine. The event of rheumatoid arthritis was non-serious, moderate in severity and not related to vaccine. This case occurred 500 days after the last dose of HEPLISAV and was reported spontaneously after the trial specified reporting period.

In the ENGERIX-B group, there was one event of rheumatoid arthritis. This event was not serious, mild in severity and considered not related to vaccine. In both the pivotal Phase 3 trials and across all trials, the rate of adverse events of special interest was lower in the HEPLISAV group than the ENGERIX-B group.

In the Phase 3 trials there were 12 adverse events of special interests and the rate was 0.21 percent

for HEPLISAV and 0.37 percent for ENGERIX-B, yielding a relative risk of 0.57 and an upper bound of the 95 percent confidence interval of 1.91. Across all trials, there were 15 adverse events of special interests, and the rate was 0.23 percent for HEPLISAV compared with 0.35 percent for ENGERIX-B.

The relative risk for HEPLISAV was 0.64 with an upper bound of 1.88. Although a medical history of autoimmune disease was an exclusion criterion in the pivotal Phase 3 trials. Some subjects with autoimmune disease were inadvertently enrolled. Identification of such subjects usually involved recollection of a history of an adverse event of special interest after enrollment. These subjects were categorized as having a pre-existing event of special interest.

Evaluation of this population provides another perspective on safety. In the pivotal Phase 3 trials 2.3 percent of HEPLISAV subjects and 2.1 percent of ENGERIX-B subjects were identified with pre-existing events of special interest. Across all trials 2.5 percent for HEPLISAV and 1.9 percent for ENGERIX-B had pre-existing events of special interest.

Of the 15 adverse events of special interest that occurred in the entire development program, five occurred

in this population. In the pivotal trials, two of 88 subjects for HEPLISAV, or 2.3 percent, and one of 23 subjects for ENGERIX-B, 4.3 percent, reported an exacerbation of the pre-existing condition.

Across all trials, one additional exacerbation occurred in the HEPLISAV group. And the rates were 2.8 percent and 3.7 percent. One subject in the HEPLISAV group experienced a new onset adverse event of special interest. This was the subject from Trial 16 who developed a vitiligo.

The subject had a pre-existing diagnosis of psoriasis. In both groups exacerbations were non-serious, mild to moderate in severity and considered not related to study vaccine by the investigators. Even though these events did not represent new diagnoses, all of these events were included in the analysis of adverse events of special interests.

For these events the relative risk for HEPLISAV was 0.99 with an upper bound of a 95 percent confidence interval of 8.51. The rate of adverse events of special interest and subjects with pre-existing events was similar in the HEPLISAV and ENGERIX-B groups.

The second assessment of autoimmune events was the adjudicated autoimmune events from Trial 16.

Investigators in Trial 16 were specifically trained on the use of a questionnaire based on the American College of Rheumatology classification criteria. The questionnaire was administered to every subject at every visit.

Individuals with positive questionnaires were referred for expert evaluation by an appropriate physician. If the expert evaluation led to the diagnosis of an autoimmune disease the event was submitted to an independent Safety Evaluation and Adjudication Committee, or SEAC. The SEAC was chaired by Dr. Poland.

The SEAC was established to increase the specificity of the assessment of events as autoimmune. It included two experts in autoimmune disease, including Dr. Ulrich Specks, an international expert in systemic vasculitis who is here with us today, and one expert in infectious diseases, Dr. Poland.

All members were external to Dynavax and not otherwise involved in the conduct of the trial. The SEAC was blind to vaccine group assignment and adjudicated all potential autoimmune events for both autoimmune ideology and relatedness to vaccine. The SEAC based its adjudication on the preponderance of evidence in their clinical judgment.

All evidence adjudicated by the SEAC were also

reported to the trial's Data Safety Monitoring Board, along with the adjudication result. Dr. John Modlin was a member of the Data Safety Monitoring Board and is here today. Two additional events were confirmed by the SEAC as new onset autoimmune events that were not already identified as adverse events of special interest.

The two events were hypothyroidism. Both events occurred in the HEPLISAV group, were mild in severity, and non-serious. While autoimmune thyroiditis is an adverse event of special interest, hypothyroidism is not.

The judgment of the SEAC was that the majority of new cases of hypothyroidism not otherwise specified are in fact autoimmune, with or without anti-thyroid antibodies. And therefore hypothyroidism should be considered autoimmune based on the preponderance of evidence criterion.

The relative risk was then calculated for all autoimmune events. That is, the combination of adverse events of special interest, and the two adjudicated, new onset autoimmune events in Trial 16. In the pivotal Phase 3 trials the rate of all autoimmune events was 0.26 for HEPLISAV and 0.37 for ENGERIX-B.

The relative risk was 0.72 with an upper bound of 2.29. Across all trials, the relative risk was 0.77, with

an upper bound of 2.18. Based on this analysis, the rate of autoimmune events in the HEPLISAV group was similar to the ENGERIX-B group. The third assessment of autoimmunity involved laboratory testing for auto antibodies.

Protocol specified pre- and post-vaccination testing was performed for anti-nuclear antibodies, a sensitive but relatively non-specific marker of autoimmune disease, and anti-double stranded DNA antibodies, which has a more specific association with systemic lupus erythematosus and is also of theoretical concern with oligonucleotides such as 1018 ISS that are structurally similar to DNA.

These assays were performed in both pivotal Phase 3 trials and the supporting trials. In addition, following the occurrence of ANCA associated vasculitis in the two subjects in Trial 10, testing of all other subjects' available sera was conducted for c-ANCA and p-ANCA. Changes in ANA were similar between the vaccine groups. Among subjects with a negative pre-vaccination ANA titer, the percentage of subjects converting to a positive titer was 5.7 percent for HEPLISAV and 5.3 percent for ENGERIX-B.

The relative risk of conversion in the HEPLISAV group was 1.10, with an upper bound of 1.49. Among subjects with a positive pre-vaccination titer, 15.4

percent for HEPLISAV and 16.8 percent for ENGERIX-B had a rise in titer. The relative risk for HEPLISAV was 0.92 with an upper bound of 1.55.

The rates of anti-double stranded DNA changes were also similar between groups. Among subjects with a negative pre-vaccination anti-double stranded DNA result, 1.2 percent for HEPLISAV and 0.9 percent for ENGERIX-B converted to a positive post-vaccination result. The relative risk of conversion was 1.29 with an upper bound of 2.56.

ANCA was assayed by a two-step process, using screening ELISA for anti-protein H3 and anti-myeloperoxidase followed by a confirmatory immunofluorescence assay for ANCA on any sample that had positive ELISA results. None of these subjects had a positive ANCA result.

In the HEPLISAV group, three individuals had positive pre-vaccination ELISA tests but negative confirmatory IFA. In the ENGERIX-B group, two individuals had positive pre-vaccination ELISA tests but negative confirmatory IFA. The HEPLISAV group and the ENGERIX-B group were similar for all autoantibodies tested.

Overall, HEPLISAV exhibited a safety and tolerability profile similar to ENGERIX-B. HEPLISAV was

well tolerated with a similar rate of post-injection reactions as ENGERIX-B. The most common post-injection reaction in both groups was injection site pain. Rates of adverse events and serious adverse events were similar between the groups.

Comprehensive analysis of autoimmune events were performed, and every analysis showed similar rates of autoimmune events and autoantibody conversion in the HEPLISAV group, compared to the ENGERIX-B group. The safety of HEPLISAV is similar to ENGERIX-B.

Dr. Poland will now discuss the benefit-risk profile of HEPLISAV which supports its use for the prevention of hepatitis B infection.

DR. POLAND: A success of 20 years of hepatitis B vaccination may create the perception that there isn’t a need for a new hepatitis B vaccine. The reality of 38,000 new infections per year in the United States demonstrates a significant need in adults. The need is greatest in groups with reduced responses to vaccines, including older adults, men, and persons with diabetes.

Because most people require all three doses of the current vaccines to develop seroprotection, large proportions of subpopulations at high risk and with poor adherence rates are unprotected from infection. In

pediatrics, hepatitis B vaccination is universal. Programs exist to facilitate such vaccination, and school requirements mandate vaccination.

In contrast, among adults hepatitis B vaccination is risk based. There are no established vaccination programs, and completion of vaccination depends on the individual's ability to return for all three doses over a six-month time period. The benefits of HEPLISAV given in a two-dose regimen over one month have been demonstrated in two pivotal, Phase 3 clinical trials as you have heard.

In fact, HEPLISAV met the primary objective of non-inferiority in two pivotal Phase 3 trials against the comparator vaccine, ENGERIX-B. HEPLISAV induced higher peak seroprotection rates than ENGERIX-B in both trials. HEPLISAV induced higher peak seroprotection rates than ENGERIX-B in every subpopulation evaluated, including populations who are known to be hyporesponsive to current vaccines.

HEPLISAV also induced higher seroprotection than ENGERIX-B at early time points, meaning that protection is obtained in one to two months rather than six or more months. This may be important for travelers and health care workers or other persons at immanent risk for hepatitis B infection.

Note that the advantages of a two-dose regimen over a three-dose regimen are not trivial. Data from the vaccine safety data link study previously cited showed that 17 percent of persons who received dose two did not receive dose three, which is required for effective seroprotection with the current vaccines. In 18 to 29 year olds, adherence was even lower, with 21 percent not receiving the final dose.

The benefits of HEPLISAV over ENGERIX-B are notable, and they are achieved without an increase in risk. The demonstrated risks of HEPLISAV fall into two categories, risks that are generally associated with intramuscular injection, and specific risks of HEPLISAV. Intramuscular injections commonly cause injection site pain and less frequently syncope. The demonstrated risks of HEPLISAV are largely post-injection reactions. The rate of local and systemic post-injection reactions was similar to that of ENGERIX-B.

The potential risks of HEPLISAV are similar to those of other hepatitis B vaccines. The Institute of Medicine found a causal relationship between anaphylaxis and current hepatitis B vaccines in yeast-sensitive individuals at a rate of about 1.1 per million doses. Because the antigen used in HEPLISAV is manufactured using

yeast, HEPLISAV is proposed to be contraindicated in persons with an allergy to yeast. This is consistent with other hepatitis B vaccines that are manufactured using yeast.

There are limited data on the use of HEPLISAV in pregnant women. Therefore, safety and immunogenicity in pregnant women have not been established. Given these limitations, a proposed category B label is considered appropriate. The fact that the Phase 3 studies showed no difference in safety between HEPLISAV and ENGERIX-B is reassuring. However, we all know that rare events coincidental or not may occur with wider use. Therefore, careful post-marketing pharmacovigilance will be important.

Hepatitis B remains an important public health problem in adults in the United States and clinicians need another option for persons at risk of infection. The immunogenicity results clearly show that HEPLISAV will improve seroprotection in adults with significantly better SPRs in all populations, including populations known to be hyporesponsive to the current vaccines.

The two-dose, one-month schedule is not only more convenient but will improve adherence, which is important for all populations but is especially needed for younger persons than some high risk groups. These benefits are

achieved without increasing risk because the safety profile of HEPLISAV is similar to ENGERIX-B.

As with any new product, the safety profile will continue to be refined during the post-marketing period. But it is good to see odds ratios below one for the majority of events of interest. Given the totality of the data and assessments, my personal conclusion is that the benefit-risk ratio for adults who need vaccination against hepatitis B favors HEPLISAV. It has the potential to lower rates of infection across the board for at-risk adults making a substantial contribution to the public health.

Dr. Martin will now provide some concluding remarks.

DR. MARTIN: Thank you, Dr. Poland. The trials presented here today represent only part of the HEPLISAV clinical program. Dynavax is committed to conducting additional trials to further inform clinicians and patients on the best use of HEPLISAV. In addition to the trials presented today, Dynavax has completed five trials, including a pivotal trial, in more than 750 chronic kidney disease patients, comparing a three-dose HEPLISAV schedule at zero, one and six months to the eight-dose ENGERIX-B schedule at zero, one, two and six months.

These trials will be submitted to the FDA as a

supplemental BLA following the approval of this BLA. In addition, after approval trials will be initiated in other special populations, such as persons with HIV infection or chronic liver disease. Following approval of HEPLISAV in Europe, an adolescent trial will begin, and the results of that trial will guide further pediatric development.

Trials will also be initiated to evaluate concomitant use with other commonly used adult vaccines. Finally, Dynavax is committed to careful pharmacovigilance. In addition to the routine pharmacovigilance conducted by all companies with approved vaccines, Dynavax has proposed a pharmacovigilance study be conducted within a medical care organization using the organization’s claim database to identify medically significant events.

Our proposed trial design has evolved since our BLA was submitted in April. We propose a design which will use risk interval analysis within the HEPLISAV cohort as one method for signal detection, and the case control design with three matched controls for each HEPLISAV recipient to provide a second method for signal detection. The medical care organization estimates they would vaccinate approximately 10,000 adults without chronic kidney disease with HEPLISAV annually.

We have proposed the first analysis should occur

when 5,000 HEPLISAV recipients are evaluable. This study, using two sources of signal detection in a medical care organization, expected to accrue 10,000 HEPLISAV recipients annually, will allow ongoing careful evaluation of HEPLISAV in a post-marketing setting in addition to ongoing standard vaccine pharmacovigilance. In three years, 30,000 HEPLISAV recipients would be evaluated in this system.

The challenges in vaccinating at-risk adults are identifying at-risk individuals in whom to initiate vaccination, then making certain that each individual actually completes the series. Unfortunately, a substantial portion of adults who manage to complete all three series of the current vaccines remain unprotected because immunogenicity is insufficient.

HEPLISAV addresses the challenges of adherence and immunogenicity. HEPLISAV delivers improved seroprotection in adults with a shorter, two-dose, one-month schedule and a safety profile that is similar to ENGERIX-B. HEPLISAV is an important new option for adults at risk of hepatitis B infection. Thank you.

DR. DAUM: Thank you very much. Let the record show that 60 minutes have not elapsed. There are about 25 seconds left to go to 60 minutes, and that is a feat of agility in my book. I would like to ask the committee at

this point if they have clarifying questions on things that they have heard. There are obviously many issues that could be discussed, but we will have time to do that a little later. We will call on Dr. Hudgens first for clarifying questions.

DR. HUDGENS: I would just like clarification on slide 81 again. I think what was proposed was different from what was in the briefing document, and it would be nice to hear it a second time.

DR. MARTIN: At the time that we submitted the BLA, in April, we were concerned about the potential for biased administration of HEPLISAV to perhaps older and more ill patients than ENGERIX-B, and so we were anticipating a randomized design. In discussion with the medical care organization, they advised that was not possible to do within their system so we have moved to this sort of a design. We do think it is important to have the initial analysis at 5,000 patients.

The current database is about 5,000. That would allow for an important interim look. But a total database of 30,000 is what we are currently thinking of. 30,000 gives reliable power to detect events that occur at a frequency of one in 10,000. So we propose that as the complete sample size for the trial. But it is different

than what was submitted in our BLA.

DR. MURPHY: Can you share with us the number of subjects in the 60 to 70 year old age group for both vaccines?

DR. MARTIN: We will be able to get that information for you after the break.

DR. MURPHY: Thank you. That is a really important population.

DR. MC INNES: I have a question about slide number 30. It is curiously worded: received all active study injections. Could you tell me the numbers of people? I understand the third dose was placebo, for HEPLISAV. Could you tell me the number of people who received, or the percentage who received all three study vaccines, including placebo?

DR. MARTIN: We can get that for you after the break.

DR. WHARTON: I appreciate the data that have been shown that demonstrate the immunogenicity in the new product compared to ENGERIX in the different populations which may have suboptimal responsiveness to current hepatitis B vaccines. Are there data on individuals who already have not responded to a series of currently available hepatitis B vaccines?

DR. MARTIN: We do have results from such a study, which I would be happy to show now, or we could show during the discussion period, whatever the Chair would prefer.

DR. DAUM: If you have them handy, we could show them now.

DR. MARTIN: Can we show the results from study two please? Study two was an early study that we conducted in first responders and health care workers in Canada who had failed at least one prior round of vaccine. That population was given a single injection of either HEPLISAV or ENGERIX-B, and then they were followed for a total of 52 weeks.

There was also in the slide show, or the image shows the results from that study, it was more than 50 percent for HEPLISAV had an antibody concentration greater than 10 at four weeks post, and it was more than 80 percent had an antibody concentration greater than 10 at week 28.

The HEPLISAV group also responded, or the ENGERIX-B group also responded to a single dose of vaccine, but it was at a lower rate. This was a rather small study, and so this is just our first hypothesis-generating look at this population.

DR. GELLIN: So now that you brought up single

dose, do you have immunogenicity data on the broader population who received a single dose? We see the second dose, but you don't know what the trajectory would be if people were lost at follow up and then found a year later.

DR. MARTIN: May I have the results from study eight please? In study eight we looked at two different schedules of HEPLISAV, one that looked at a zero and four week schedule, one at a zero and eight week schedule. It was one of our regimen defining studies as we were conducting the trial. This is in young adults.

And the results from that study showed that following a single dose of vaccine, the zero eight group, at week eight -- that is after only one dose of vaccine -- the SPR in that group at week eight, so eight weeks after a single dose of vaccine in young adults, was greater than 80 percent.

DR. GELLIN: But you do not have data of single dose over a longer period of time?

DR. MARTIN: No, we don't, Dr. Gellin. That is because this was designed as a two-dose regimen. So all I have is that window where we looked at eight weeks between dose. That is the only information that I have.

DR. DAUM: So my question goes to the necessity for this adjuvant. And do you have data? What prompted

the company to put the adjuvant in the vaccine? Do you have data on two doses or any of the doses without the adjuvant?

DR. MARTIN: In our Phase 1 trial we included one group that had no adjuvant, and that group did not perform as well as either the alum adjuvanted vaccine or various concentrations of 1018 ISS. We looked at concentrations of 1018 ISS as low as 300 micrograms, and ranged up to 3,000, which is the dose that we have taken forward.

DR. DAUM: Are we going to be able to see those data?

DR. MARTIN: I can show you the data for the groups that received the various doses of ISS. But I don’t have the data here for the group that received unadjuvanted vaccine. I don’t have that information.

DR. DAUM: Other clarifying questions? These are obviously issues that we can discuss later, after we hear from the FDA this afternoon, but other clarifying questions for now? Okay, in their absence I propose that we take a break.

DR. MARTIN: Dr. Daum, if you would like I do have the results on the three-dose injection for HEPLISAV that is the percentage who received the placebo injection. Would you like me to show that?

DR. DAUM: If you can get them up quickly that would be great.

DR. MARTIN: 97 percent of the HEPLISAV group and 97.4 percent of the ENGERIX-B group received all three injections.

DR. DAUM: I think that was in the packet.

DR. MARTIN: It was a question that we were supposed to address. I just wanted to clarify it.

DR. DAUM: Good, thank you. We will now take a break. I have 10:00 sharp in the Eastern Time Zone. We will reassemble at 10:15 and hear the FDA presentation. Thank you.

(Brief recess)

Agenda Item: FDA Presentation

DR. DAUM: Having heard the sponsor's presentation we will now hear the FDA's presentation. Their feat will require less agility in that there will be two speakers in the same amount of time. Dr. Worobec, welcome. Why don't you begin, and then Dr. Smith will speak next. Thank you.

DR. WOROBEC: Good morning. Advisory Committee members, honored guests, and colleagues at Dynavax and FDA, my name is Dr. Alexandra Worobec and I will be presenting a review of immunogenicity for the recombinant adjuvanted

hepatitis B vaccine, HEPLISAV.

In my presentation this morning I will be discussing the proposed indication for HEPLISAV, the use of seroprotection rate as an effectiveness endpoint. We have heard about this already this morning from both Dr. Major and from Dynavax. I will also discuss the basis of dose selection of the 1018 ISS adjuvant. In the latter part of my talk I will discuss the Phase 3 studies of HEPLISAV, DV2-HBV-10 and DV2-HBV-16, with an emphasis on trial design and immunogenicity results.

The proposed indication for HEPLISAV is for the active immunization against all subtypes of hepatitis B infection for adults 18 to 70 years of age. The dosage and administration is that of a 0.5 ml dose that contains 20 microgram of recombinant hepatitis B surface antigen, which is combined with 3,000 micrograms of the 1018 ISS adjuvant, to be given in a schedule of two doses given intramuscularly one month apart. In other words, at month zero and at month one.

To reiterate the discussion of seroprotection rate for the evaluation of hepatitis B vaccine effectiveness, the SPR is defined an anti-hepatitis B surface antigen level of 10 milli International Units per ml or greater, and is recognized as conferring protection

against hepatitis B virus infection.

Important to note are that higher absolute levels of anti-hepatitis B surface antigen antibodies are not indicative of a higher degree or necessarily a longer duration of protection among responders.

Now I would like to focus your attention on what the dose selection of 1018 ISS adjuvant was based on. A pilot study, DV2-HBV001, had evaluated escalating doses of the 1018 ISS adjuvant of 300, 650, 1,000 or 3,000 micrograms, which was formulated with a fixed dose of the recombinant hepatitis B surface antigen of 20 micrograms, and was tested in a population of hepatitis B surface antigen seronegative healthy adults who were 18 to 55 years of age.

Results of this study had shown that two IM doses of the recombinant hepatitis B surface antigen, 20 micrograms, combined with 3,000 micrograms of the 1018 ISS adjuvant, yielded the highest SPR rate and had an acceptable safety profile.

Now I would like to focus your attention on the two Phase 3 studies of HEPLISAV, DV2-HBV-10 and DV2-HBV-16. Similar study designs were used for both of the Phase 3 studies, 10 and 16. Importantly, both studies were subject and observer blind, randomized controlled study designs.

ENGERIX-B from GSK Biologicals was used as the active comparator.

Enrolled subjects were seronegative for hepatitis B surface antigen, anti-hepatitis B surface antigen antibody, which was defined as a level less than 5 milli-International Units per ml, and were negative for anti-hepatitis B core antigen antibody, and had never received any prior hepatitis B vaccine. Excluded individuals included those at high risk for recent exposure to hepatitis B virus, hepatitis C virus, or HIV.

For both of these studies, three injections were given to study subjects. For HEPLISAV these were administered at weeks zero and four, with saline placebo given at week 24. And for ENGERIX-B, vaccine was administered at weeks zero, four and 24, also known as month six.

Now I would like to discuss Study DV2-HBV-10. This study was conducted in 21 sites in Canada and Germany, subjects 11 to 55 years of age were enrolled with subjects 18 to 55 enrolled in Germany. Subjects were randomized three to one to HEPLISAV to ENGERIX-B. And a total of 2,415 subjects 18 years of age and older were enrolled, with 1,809 subjects randomized to HEPLISAV, and 606 subjects randomized to ENGERIX-B.

The primary immunogenicity endpoint for this study was a seroprotection rate up to the final act of injection. And the primary immunogenicity analysis evaluated a difference in the seroprotection rate between ENGERIX-B at week 24, or four weeks after the last active dose, and HEPLISAV at week 12, or eight weeks after the last active dose.

It is important to note that this study was not done under IND, and thus the FDA did not have input into its study design. The success criteria for the study was met if the HEPLISAV SPR was considered non-inferior to ENGERIX-B, if the upper limit of the two-sided 95 percent confidence interval on the difference in SPRs for ENGERIX-B minus HEPLISAV was less than 0.1 percent, or less than 10 percent.

In addition, there were a number of other immunogenicity endpoints evaluated in the study DV2-HBV-10, which comprised the seroprotection rate and geometric mean antibody concentrations, or GMCs, for HEPLISAV versus ENGERIX-B at other study time points which ranged from weeks four through week 28.

The immunogenicity analysis population consisted of the following -- first, the per-protocol population, which was defined as subjects who had met eligibility

criteria, had no major protocol violations, they would have had to have received all protocol specified study injections, and anti-hepatitis B surface antigen measurements, and all injections needed to have been obtained within pre-specified windows.

This was a more stringent subject population and was used for the primary immunogenicity analysis. In addition, a modified intent to treat population was evaluated for immunogenicity, which included subjects who had received at least one study injection and had one post-baseline anti-hepatitis B surface antigen level. This was used extensively for subgroup analyses and for the integrated summary of efficacy.

I would like to run through the subject demographics, which we have already heard earlier this morning. Similar demographic and baseline characteristics were seen in both HEPLISAV and ENGERIX-B groups. Most subjects were white or non-Hispanic Latino.

The mean age of subjects was approximately 40 years, slightly more females than males were enrolled in the study, and the majority of subjects, in fact greater than 99 percent of subjects, were considered seronegative or had anti-hepatitis B surface antigen levels at baseline that were less than 5 milli-International Units per ml.

Because this study also sought to look at certain other demographic groups that might be considered as hypo-responders, the study also looked at, in an exploratory analysis, non-smokers, smokers, diabetic subjects, and obese subjects. For these particular subgroups, the majority of subjects enrolled in Study 10 were non-smokers, were non-diabetic and were non-obese.

For the subject disposition, a total of 2,428 subjects were enrolled. Again, 1,809 adult subjects 18 years and older were assigned to HEPLISAV, 606 adults were assigned to ENGERIX-B. Approximately 97 percent of all adult subjects completed this study. And the most common reason for subject discontinuation was being lost to follow-up, reported in 1.7 percent of subjects in each group.

For this study, enrollment also included 13 adolescents, defined as those younger than 18 years of age. And for this population, 11 subjects were assigned to HEPLISAV, two were assigned to ENGERIX-B, and these were importantly not included in the immunogenicity analysis.

I would like to now focus your attention on a discussion of the primary immunogenicity endpoint analysis for Study DV2-HBV-10. This again was the seroprotection rate for HEPLISAV measured at week 12 when compared to that

of ENGERIX-B measured at week 28, using the per protocol analysis population for adults 18 to 55 years of age.

We see here that at these time points HEPLISAV had an SPR of 95 percent, versus that of 81 percent for ENGERIX-B, and the non-inferiority criteria were met for this primary endpoint. There were some additional endpoints evaluated in Study DV2-HBV-10 that comprised an evaluation of SPRs and GMCs at the different study visits. And I will now present, just run through the data for the SPRs, and partly because I would like to illustrate the kinetics of the seroprotection rate over time.

And these, again, are comparisons of HEPLISAV, which is administered at weeks zero and four, with placebo given at week 24, and ENGERIX-B given on weeks zero, four, and 24. So at week four we see relatively low SPRs for both treatment groups. By week eight, HEPLISAV has increased to about 88.5 percent. But it is important to keep in mind that at week four and at week eight, ENGERIX-B enrolled subjects have not completed all of their vaccinations.

In fact, at week four only one dose of ENGERIX-B would have been given to study subjects. Importantly, though, at week 28, which is the last time point in the study, we see that the seroprotection rates are fairly

similar between the two treatment groups, with 97.9 percent versus 81 percent of subjects having demonstrated seroprotection rates.

And similar results were seen for the GMCs, the geometric mean concentrations, at these varying time points, again, at week four I don’t think for either group would be considered seroprotective. And at week eight we see an increase in HEPLISAV. And at week 28, both groups are quite comparable, with 320 and 348 milli-International Units for the ENGERIX-B group seen at the final time point.

So in conclusion for Study DV2-HBV-10, HEPLISAV met pre-specified non-inferiority criteria for immunogenicity, as compared to the licensed active comparator hepatitis B vaccine, ENGERIX-B. And while I didn’t show these data, the findings for the modified intent to treat population paralleled that for the per protocol population, which was important from our standpoint in terms of validating the data.

Now I would like to shift our attention to the second Phase 3 study, Study DV2-HBV-16. For this study, subjects 40 to 70 years of age, so slightly older, were enrolled into the study. At 32 sites in the United States and Canada, and randomization was stratified by age, 40 to 49 years, 50 to 59 years, and 60 to 70 years, and

randomization was also stratified by study site.

This was a longer trial than Study 10, with a study duration of 52 weeks after the first dose of vaccine given. In addition, this study sought to evaluate lot consistency of three different manufactured lots of HEPLISAV. So subjects here were randomized to one of the three consistency lots of HEPLISAV, an earlier lot of HEPLISAV or ENGERIX-B.

A total of 2,452 subjects were randomized with 1,969 randomized to HEPLISAV and 483 randomized to ENGERIX-B. For this study there were two co-primary immunogenicity endpoints. First there needed to be demonstration of HEPLISAV lot consistency between the three lots. If these criteria are met, then the second endpoint was a comparison of the seroprotection rate between the two vaccine arms eight weeks after the final act of injection.

So this differed somewhat from the previous study and the time point after measurement of immunogenicity for ENGERIX-B was slightly different. So the primary immunogenicity analysis was the difference in the seroprotection rate between ENGERIX-B group at week 32 or eight weeks after the last active dose, and HEPLISAV at week 12, or eight weeks after the last active dose.

Non-inferiority between the two groups was

established if the lower limit of the two-sided 95 percent confidence interval of the difference in seroprotection rate, or the seroprotection rate for the three combined HEPLISAV lots at week 12, minus ENGERIX-B measured at week 32 was greater than minus 10 percent.

Again, there were additional immunogenicity endpoints studied for Study DV2-HPV-16, which comprised seroprotection rates and GMC measurements for HEPLISAV versus ENGERIX-B at all other study time points, which ranged from weeks four all the way through week 52.

The immunogenicity analysis populations were similar to Study 10. And again, I would just run through this. The non-inferiority per protocol population for this study comprised subjects who received one of the three consistency lots of HEPLISAV or ENGERIX-B, received all three protocol-specified study injections, had no major protocol violations. And anti-hepatitis B surface antigen measurements in all injections were required to have been obtained within pre-specified windows.

Again, the modified intent to treat, subject population comprised those who received at least one study injection, and had one post-baseline anti-hepatitis B surface antigen level. Subject demographics for this study were also similar to that seen in Study 10 with a few minor

caveats. There were similar demographic and baseline characteristics between HEPLISAV and ENGERIX-B. Most enrolled subjects were white or non-Hispanic Latino. The mean age was slightly older at age 54, because subjects enrolled here were older.

Again, there was a slightly higher percentage of females enrolled than males, and more than six percent of subjects had anti-hepatitis B surface antigen levels of less than five milli-International Units per ml, or were seronegative. And again, the majority of enrolled subjects were non-smokers, were non-diabetic, or were non-obese.

In terms of the subject disposition, 2,452 subjects were enrolled, 1,969 subjects were assigned to HEPLISAV, 483 subjects were assigned to ENGERIX-B. The non-inferiority per protocol population comprised 1,872 subjects or about 76 percent of the randomized population. And the reason for this is because this number was actually lower than those who actually got all the injections.

The reason being, again, to be included in this population you had to have gotten injections within pre-specified time intervals, et cetera. Those were the most common reasons why an individual would not be considered per protocol.

92.5 percent of all randomized subjects completed

this study. And again, the most common reason for subject discontinuation was lost to follow up, reported in about 3.8 percent of subjects.

A review of the primary immunogenicity endpoint analysis for Study 16 showed, again, we want to point out that HEPLISAV was given on weeks zero and four, with placebo given at 24, and ENGERIX-B administered at weeks zero, four and 24. And looking at the seroprotection rate, eight weeks after the last dose for each respective treatment arm, the SPR for HEPLISAV was 90 percent, versus 70.5 percent for ENGERIX-B. And again, non-inferiority criteria were met.

Importantly here, also, I wanted to mention, although I am not presenting the data because it is not germane to our discussion this morning, lot to lot consistency criteria were met for the three lots of HEPLISAV. So basically, the two co-primary endpoints were met for this study.

Just running through the select seroprotection rates by visit, again, trying to show the kinetics of the immune response, for the per protocol population in adults 40 to 70 years of age, we see here again that by week four the SPRs are not terribly high. By week eight they have gotten higher for HEPLISAV.

And as we go on in the study, by week 52 they are 92 percent, versus 59 percent for ENGERIX-B. And for HEPLISAV we see that basically from week 12 onward they have remained 90 percent or greater. Again, also for a review of the select GMCs, not for every time point but just for certain time points for this study, because we really didn't have room on the slide, for the per protocol population we again see at early time points low GMCs.

At week four they were below what we would consider a seroprotective level. But from about week eight onward for HEPLISAV we are in the protective range. And again, taking into account that GMCs are not indicative of necessarily greater protection and a finding of higher GMCs above a protective cut-off is not necessarily a major consideration in determining effectiveness of a hepatitis B vaccine, we see that by week 52 both HEPLISAV treated subjects and ENGERIX-B subjects would be considered protected, based on the cut-off of 10 milli-International Units per ml.

So in conclusion, for Study 16, HEPLISAV met pre-specified, non-inferiority criteria for immunogenicity, as compared to the licensed active comparator hepatitis B vaccine, ENGERIX-B. And findings for the modified intent to treat population, again, not shown due to time

constraints, paralleled those of the per protocol population.

Our overall conclusions for both of the Phase 3 studies show that the seroprotection rate following two doses of HEPLISAV was non-inferior to the seroprotection rate induced by three doses of ENGERIX-B. High seroprotection rates, 90 percent or greater, against hepatitis B were evident eight weeks after the second dose of HEPLISAV or at week 12.

And while I didn’t show the subgroup analyses for HEPLISAV, HEPLISAV immunized subjects did not reveal clinically significant differences between antibody responses in younger and older subjects, or between males and females. Again, in HEPLISAV treated subjects.

And conclusions could not be drawn regarding differences among ethnic and racial subgroups since the majority of subjects enrolled were Caucasian, although seroprotection rates were similar among all ethnic groups examined. Thank you. I will take questions.

DR. DAUM: I would prefer it if we would go on with Dr. Smith’s presentation, and then have questions for both of you.

DR. SMITH: Good morning everyone. I am Lorie Smith, and I am going to be discussing the review of

safety. I will discuss the safety data from the Phase 3 trials DV2-HBV-10 and DV2-HBV-16. I will discuss the key points from the integrated analysis of safety in Phase 3 and supportive trials. I will summarize the safety review, and present the pharmacovigilance plan proposed by Dynavax.

A total of 5,845 subjects were included in the overall safety population. There were a total of 4,864 individuals from the Phase 3 trials, which included 3,777 HEPLISAV and 1,087 ENGERIX-B recipients. An additional 981 individuals from the supportive trials were included. 648 were HEPLISAV recipients and 333 were ENGERIX-B recipients.

The follow up periods for adverse events was 28 weeks for both Phase 3 trials. Subjects were followed for serious adverse events, for a period of 28 weeks in study DV2-HBV-10, and for 52 weeks in study DV2-HBV-16. Supportive trials included controlled and uncontrolled studies, and the safety follow up periods for these trials varied, as noted here.

I will now move on to discuss the Phase 3 trials, beginning with study DV2-HBV-10. The primary safety objective of this trial was to demonstrate the safety and tolerability of vaccination with HEPLISAV when administered to adolescent and adult subjects. The safety population consisted of all subjects who received at least one study

injection and had any post baseline safety data.

2,415 adults and 13 adolescents were included in the safety population -- 1,809 adults and 11 adolescents in the HEPLISAV group and 606 adults and two adolescents in the ENGERIX-B group. Safety assessments consisted of solicited reactions evaluated for seven days after each injection, adverse events and serious adverse events evaluated for 28 weeks after the first injection, which is 24 weeks following the last active injection of HEPLISAV.

Anti-nuclear antibody and anti-double stranded DNA was evaluated at baseline and 28 weeks. With regard to solicited local reactions, pain, redness and swelling were reported by more subjects receiving HEPLISAV than ENGERIX-B after both active doses of HEPLISAV. Please note that a comparison between the third active dose of ENGERIX-B and the placebo injection for HEPLISAV recipients is not shown in the solicited adverse event tables in this presentation.

With regard to solicited systemic reactions, fatigue, headache and malaise occurred with similar incidents among treatment groups after both active injections of HEPLISAV. 60.5 percent of subjects in the HEPLISAV group reported at least one unsolicited adverse event. 10.6 percent reported a severe event. 62 percent of subjects in the ENGERIX-B group reported at least one

unsolicited adverse event, 14.4 reported a severe event.

Specific, unsolicited adverse events will be discussed in the context of the integrated summary of safety. No deaths were reported for the 28 week duration of this trial. All non-fatal SAEs occurred in adult subjects. 1.5 percent of HEPLISAV recipients and 2.1 percent of ENGERIX-B recipients reported at least one serious adverse event.

Three SAEs were identified as auto-immune adverse events, and will be discussed further here. Other specific serious adverse events will be discussed in the context of an integrated summary of safety.

In the HEPLISAV group, one subject was diagnosed with c-ANCA positive vasculitis, specifically, Wegener’s granulomatosis. And one subject was diagnosed with Guillain-Barré syndrome. In the ENGERIX-B group, one subject was diagnosed with a p-ANCA positive vasculitis.

Wegener’s granulomatosis occurred in a 55 year old female with no significant past medical history, who developed widespread urticaria 18 days after injection one. She received injection two as schedule, approximately one month later. Recurrent sinusitis began approximately two and one-months after injection one, which is one and one-half months after injection two.

She developed pulmonary infiltrates, pleural effusions and glomerulonephritis approximately seven months after injection one, at which time serologic testing for ANCA yielded a positive c-ANCA and Wegener's granulomatosis was diagnosed. She received treatment with corticosteroids and cyclophosphamide and was determined to be clinically stable four months after diagnosis. The investigator assessed this event as possibly related to study treatment.

Her serum was retrospectively analyzed for ANCA. At her screening visit her ANCA was negative. Four weeks after dose one her ANCA to protein 3 became weakly positive. Twelve weeks after dose one, which was eight weeks after dose two, her ANCA to PR3 was positive, and 23 weeks after dose one, which was 19 weeks after dose two, her ANCA to PR3 became strongly positive and remained so at week 28.

Guillain-Barré Syndrome occurred in a 36 year old female with a past medical history of splenectomy performed for unknown reasons. She received an inactivated influenza vaccine 105 days after HEPLISAV injection two. Five days later she developed an ascending weakness that progressed to respiratory failure and she was diagnosed with Guillain-Barré syndrome. Her course was complicated by papillary carcinoma of the thyroid and bilateral pulmonary emboli.

The investigator assessed this event as probably not related to study treatment.

p-ANCA positive vasculitis occurred in a 44 year old female with a past medical history that included mixed connective tissue disease, osteoarthritis, food allergy, and headache. She developed fever and malaise three months after her second injection of ENGERIX-B. 127 days after the second injection, she developed a pulmonary hemorrhage and had a positive p-ANCA, leading to the diagnosis.

Of note, her history of mixed connective tissue disease was undisclosed at enrollment. Her baseline ANA was greater than one to 5,120, and ANCA testing of banked serum was negative until the time of diagnosis. The investigator assessed this event as not related to study treatment.

With regard to laboratory investigations, ANA was performed at baseline in week 28 in this study. Most subjects had ANA titers less than the one to 160 threshold at baseline and at week 28. ANA results were comparable among treatment groups for each serial dilution. 2.9 percent of HEPLISAV recipients and 3.3 percent of ENGERIX-B recipients experienced an increase in ANA titer, and most of these were a one dilution increase.

Anti-double stranded DNA was also evaluated at

baseline and week 28. As you can see here, the majority of subjects in each treatment arm had a negative anti-double stranded DNA at baseline, and a similar proportion of subjects in each group converted from a negative result at baseline to a positive result at week 28.

ANCAs were evaluated retrospectively on banked serum from 1,780 HEPLISAV and 596 ENGERIX-B recipients in this study. Three HEPLISAV recipients and two ENGERIX-B recipients had positive ANCA by ELISA. None of these subjects had positive ANCA by immunofluorescence.

So in summary, there were a higher rate of injection site reactions in the HEPLISAV group in this study, but most were mild. There were similar rates of solicited systemic reactions, unsolicited adverse events, and serious adverse events. There were no clinically important differences in ANA titers or anti-double stranded DNA levels.

There were two cases of ANCA positive vasculitis, one in each treatment group. Therefore, subsequent studies contained an algorithm to capture autoimmune adverse events, or AIAEs, in which suspected AIAEs were referred to a Safety Evaluation and Adjudication Committee, the SEAC. Adverse events of special interest including selected neuroinflammatory, musculoskeletal, gastrointestinal,

metabolic, skin, and autoimmune diseases, were also captured in subsequent studies.

I will now move on to discuss trial DV2-HBV-16, the other Phase 3 trial. The safety objectives of this trial were to demonstrate the safety of HEPLISAV in healthy subjects 40 to 70 years of age, and to compare the safety profile of HEPLISAV to that of ENGERIX-B in this population. The safety population consisted of individuals who received at least one study injection and had any post-baseline safety data.

2,449 subjects 40 to 70 years of age were included in the safety population. 1,968 were in the HEPLISAV group, and 481 were in the ENGERIX-B group. Within the HEPLISAV group, 1,439 subjects were randomized to receive one of three consistency lots, and 529 subjects were randomized to receive Lot TDG006, which is an older lot used in some of the earlier studies.

Safety assessments included solicited reactions evaluated for seven days after each injection. Adverse events were followed for 28 weeks after injection one, which was 24 weeks after the last active dose of HEPLISAV.

Subjects were followed for SAEs, AESIs, which again is adverse events of special interest, and potential autoimmune adverse events, for 52 weeks after injection

one, which is 48 weeks after the last active dose of HEPLISAV. And again, any potential autoimmune adverse events were sent to the SEAC for adjudication. Serum chemistry and hematology were performed at baseline, weeks four, eight, 24 and 28 weeks. ANA and anti-double stranded DNA were evaluated at baseline and 52 weeks.

So this table summarizes the solicited local reactions. Redness was reported by more subjects receiving lot TDG006 than by subjects receiving either the consistency lots or ENGERIX-B. Swelling occurred with a similar incidence in each group after both active HEPLISAV injections. Pain was reported by more HEPLISAV recipients than ENGERIX-B recipients after both active HEPLISAV injections.

With regard to solicited systemic reactions, malaise, headache, myalgia and fatigue all occurred with similar incidence among treatment groups after both active injections of HEPLISAV. 25.2 percent of subjects in the HEPLISAV consistency lot group reported at least one unsolicited adverse event. 4.5 percent reported a severe event. 25.1 percent of subjects in the HEPLISAV lot TDG006 group reported at least one unsolicited adverse event. 5.9 percent were severe events.

24.7 percent of subjects in the ENGERIX-B group

reported at least one unsolicited adverse event. 5.8 reported a severe event. Specific, unsolicited adverse events will be discussed in the context of the integrated summary of safety.

There were two deaths in trial DV2-HBV-16. A 46 year old male HEPLISAV recipient with no past medical history had a fatal pulmonary embolism while playing softball 46 days after the second injection of lot TDG006. Dynavax was unable to obtain the medical records pertaining to this event.

A 64 year old male ENGERIX-B recipient with a past medical history that included hypertension and gout, was hospitalized for an acute myocardial infarction 43 days after the second injection and he died of cardiac arrest on the second day of hospitalization.

Non-fatal, serious adverse events occurred in a similar proportion of subjects in each group, and specific serious adverse events will be discussed in the context of the Integrated Summary of Safety. Dynavax conducted a prospective analysis of autoimmune adverse events in this study as noted.

There were nine events in HEPLISAV recipients initially identified by the investigator as potential autoimmune adverse events. Two of those were subsequently

determined not to be autoimmune in nature. Seven were considered potential autoimmune adverse events, and five were confirmed as such by the SEAC. Two individuals had evidence of pre-existing disease when baseline serum was evaluated. Therefore the total number of new onset, autoimmune adverse events was three.

So this table summarizes the nine adverse events identified as potential autoimmune adverse events discussed in the previous slide. Also included in this table are the time from active injection to event, followed by the assessment of the likelihood of autoimmune origin and relationship to study vaccine, as determined by the investigator, and subsequently by the SEAC.

The first three events listed are those determined by the SEAC to be new onset autoimmune adverse events. Two subjects, represented in the following two lines, had newly diagnosed hypothyroidism while on study but were found to have laboratory evidence of pre-existing hypothyroidism when banked serum was analyzed.

The case of erythema nodosum was considered not autoimmune in nature by the SEAC but related to study injection. For events determined not to be autoimmune in origin the SEAC did not assess whether the event was new or pre-existing.

Among the last four events listed, the cases of erythema nodosum, Bell’s palsy and hypothyroidism occurred in individuals with no history of disease. An individual with a history of microscopic colitis had two exacerbations of disease while on study.

Dynavax also evaluated the incidence of adverse events in individuals with pre-existing autoimmune disorders. There were 30 subjects with pre-existing autoimmune disease who were inadvertently enrolled in Study 16. Fifteen were randomized to the HEPLISAV consistency lots, eight were randomized to lot TDG006, and seven were randomized to ENGERIX-B.

Overall the adverse events and serious adverse events occurred with a higher frequency in this subgroup than in the general study population at 60 versus 51.5 percent, respectively. The frequency of adverse events and serious adverse events among this subgroup were similar when treatment groups were compared.

With regard to laboratory investigations for Study 16, hematology and serum chemistry were performed at baseline, weeks four, 24 and 28. And the results were similar across treatment groups and did not change significantly from baseline. Anti-double stranded DNA was evaluated at baseline in week 52. Most subjects had

negative results at baseline and a similar proportion converted from a negative to a positive result by week 52.

ANA was also evaluated at baseline in week 52, and most subjects had a negative ANA below the one to 160 threshold at baseline. A similar proportion of subjects in each treatment group converted from a negative baseline titer to a positive titer at week 52, and a similar proportion of subjects that began with a positive baseline titer had increased titers at week 52 in each treatment group.

So in summary, there was a higher rate of injection site reactions in HEPLISAV recipients in this study. There were similar rates of solicited systemic reactions, unsolicited adverse events, and serious adverse events between groups.

Three HEPLISAV recipients and no ENGERIX-B recipients in Study 16 reported SEAC confirmed, new onset, autoimmune adverse events. All three were deemed not related to vaccination by the SEAC. There were no clinically important differences noted in laboratory parameters.

I will now discuss key points from the Integrated Summary of Safety. This slide shows the distribution of the 5,845 adult subjects included in the integrated safety

analysis. A total of 4,425 subject received HEPLISAV. Thirteen additional subjects, age 11 to 17 years, participated in study DV2-HBV-10. And the safety data from these individuals were also evaluated as part of a comprehensive safety review.

Again, the follow up periods for the Phase 3 trials and the controlled and uncontrolled supportive trials are summarized in this slide. The baseline characteristics of subjects receiving HEPLISAV and ENGERIX-B do not suggest a selection bias based on age, sex, race, or Hispanic ethnicity.

I will now discuss the results of the ISS. With regard to laboratory investigations, hematology, serum chemistries, ANA, anti-double stranded DNA, ANCAs, complement components C3 and C4, erythrocyte sedimentation rate, and urinalyses were evaluated. And no clinically significant trends were identified post-vaccination. Please note that ANCAs were evaluated retrospectively, and the Phase 3 trial DV2-HBV-10 and in one supportive, uncontrolled trial, DV2-HBV-14.

There were two deaths in study 16, as previously discussed. No other deaths were reported for the duration of these trials. All non-fatal, serious adverse events occurred in adult subjects. 2.7 of HEPLISAV recipients and

3.7 percent of ENGERIX-B recipients reported at least one serious, adverse event. The overall incidence of unsolicited adverse events was similar between treatment groups, and most were mild to moderate in intensity.

There was a numerical imbalance in the incidence of pulmonary emboli, with five occurring in the HEPLISAV arm and none occurring in the ENGERIX-B arm. One case was fatal, as previously discussed. The remaining four occurred in individuals with underlying predisposition, as noted here.

When looking at other thrombotic events, two cases of post-operative deep vein thrombosis occurred, one in each treatment arm. One case of superficial thrombophlebitis was reported in a HEPLISAV recipient, and two cases of an unspecified thrombosis were reported in ENGERIX-B recipients. In total, the thrombotic serious adverse events and adverse events occurred in 0.2 percent of HEPLISAV and ENGERIX-B recipients as well.

Dynavax collected autoimmune adverse events prospectively only for studies 16 as noted, so no integrated analysis exists for this analysis. In addition, Dynavax searched the safety database for adverse events of special interest, which included selected neuroinflammatory, musculoskeletal, gastrointestinal,

metabolic, skin, and autoimmune disorders from a list of adverse events used in other trials, and found that 0.2 percent of HEPLISAV recipients and 0.4 percent of ENGERIX-B recipients reported adverse events of special interest.

The FDA conducted an additional analysis of events of potential autoimmune origin, and analyzed serious adverse events, adverse events of special interest, and autoimmune adverse events that were treated with immunosuppressive therapy, and found 0.2 percent of subjects in each group reported events that fell into this category.

Please note that included in this FDA analysis are the autoimmune adverse events and adverse events of special interest evaluated by Dynavax. This table summarizes the FDA analysis. Again, it’s of autoimmune adverse events, adverse events of special interest, and serious adverse events treated with immunosuppressive therapy.

This slide addresses this for HEPLISAV recipients, those events occurring in the ENGERIX-B arm will be presented in the next slide. The time from last active injection to event is listed, as well as whether or not it was an exacerbation of a pre-existing condition or a new diagnosis.

The reported background incidence rates per year for each condition are also provided. The events are listed in the table in increasing order of background incidence rate. The first event listed is Tolosa-Hunt Syndrome, a rare syndrome of painful ophthalmoplegia caused by idiopathic granulomatous inflammation of the cavernous sinus.

You will see that four events represent an exacerbation of disease, and those are noted at the bottom of the table. I would like to point out that the yes denoted in the past medical history column of the case of vitiligo indicates a past medical history of psoriasis, not vitiligo, and that is why it is not denoted as an exacerbation.

This is a similar table summarizing autoimmune adverse events of special interest and serious adverse events, treated with immunosuppressive therapy for ENGERIX-B recipients. Please note the subject with the p-ANCA positive vasculitis had a past medical history of mixed connective tissue disease. And the subject with rheumatoid arthritis had a past medical history of hand pain.

Finally, I would like to point out that the final event listed was an SAE of bronchial hyper-reactivity in an ENGERIX-B recipient but it included here because a workup

for Churg-Strauss syndrome was performed that was negative. No other individuals that received immunosuppressive therapy such as steroids for an RAD or asthma exacerbation are included in this analysis.

In addition, thyroid events were included in the FDA analysis of adverse events of potential autoimmune origin, because the most common cause of hypothyroidism and iodine sufficient countries is autoimmune thyroiditis, or Hashimoto’s thyroiditis. And the most common cause of hypothyroidism is Grave’s disease, also known as Basedow’s disease. Either can present as goiter, hypothyroidism or hyperthyroidism. An FDA analysis of all thyroid adverse events will be discussed here. And again, please note that this includes the AIAEs and AESIs evaluated by Dynavax.

The overall incidence of thyroid diseases reported as adverse events was 0.4 percent in HEPLISAV subjects, and 0.1 percent in the ENGERIX-B group. The relative risk, meaning the risk in HEPLISAV recipients relative to the risk in ENGERIX-B recipients, was 2.6 with a 95 percent confidence interval of 0.7 to 10.

All thyroid diseases and abnormal thyroid lab results that reported as adverse events occurred with an incidence of 0.4 percent in HEPLISAV recipients and 0.2 percent in ENGERIX-B recipients, with a relative risk of

1.8 and 95 percent confidence interval of 0.6 to 5.8. So this table displays all adverse events pertaining to the thyroid for subjects in the Phase 3 trials.

Those events highlighted in yellow were reported by HEPLISAV recipients. Those highlighted in the darker color were reported by ENGERIX-B recipients. If pre-existing thyroid disease, laboratory evidence of pre-existing disease, or pre-existing thyroid related symptoms were present, that is denoted in the past medical history column.

Thyroid events reported by subjects in the supportive trials are shown here. Please note that various dosing regimens were used in some of the earlier trials, so there may be a different number of columns for days after dose than you saw in the previous table.

Those events highlighted in gray are not considered to be likely to be autoimmune in nature, and are not included in the calculations for the statistical analysis. Again, the presence of pre-existing disease, pre-existing laboratory evidence of disease or symptoms is denoted in the past medical history column.

I will now summarize the safety review. The review of local and systemic solicited adverse events, deaths, and laboratory investigations did not reveal any

clinically significant differences between recipients of HEPLISAV and ENGERIX-B. Non-fatal, serious adverse events occurred with similar incidence between groups.

There was a numerical imbalance in the incidence of pulmonary emboli. The overall incidence of thrombotic events was similar between HEPLISAV and ENGERIX-B recipients. Autoimmune adverse events were evaluated prospectively, as previously noted, in study 16 by Dynavax.

Five autoimmune adverse events were identified, two of which occurred in subjects with evidence of pre-existing disease, leaving three new onset autoimmune adverse events. Dynavax also reviewed all trials for potential adverse events of special interest, and by selected MedRA preferred term, the incidence of adverse events of special interest was similar between groups.

An additional FDA analysis of other events of potential autoimmune origin included a comprehensive evaluation of all thyroid-related adverse events potentially representing autoimmune events. These were reported in a higher proportion of HEPLISAV recipients, but the confidence interval surrounding the relative risk included one.

Also included were adverse events requiring immunosuppressive therapy, and these events occurred with

similar incidence between HEPLISAV and ENGERIX-B recipients. Rare, serious, adverse events were reported among HEPLISAV recipients, and included Wegener's granulomatosis, Tolosa-Hunt syndrome, and Guillain-Barré syndrome. Rare, serious events reported among ENGERIX-B recipients included a case of p-ANCA positive vasculitis.

Limitations of the ISS specifically pertaining to autoimmune events, or that autoimmune diseases occur with a relatively rare incidence in the general population are often insidious in onset, and early symptoms are often non-specific, making the assessment of causality with vaccine receipt difficult.

In addition, large sample sizes are necessary for a statistically robust assessment of risk. For relatively infrequent adverse events, statistical variability in observed rates among 4,425 HEPLISAV and 1,420 ENGERIX-B recipients limits the ability to draw firm conclusions about vaccine attribution.

I will now present the post-licensure pharmacovigilance plan as proposed by Dynavax. As noted, this is evolving and has changed somewhat since you received the briefing document and Dr. Martin provided a more recent update earlier.

Dynavax will perform routine surveillance, which

includes spontaneous adverse event report collection, follow up and assessment, a review of the medical literature and safety information from other sources, safety signal identification and evaluation, close monitoring for adverse events of special interest. And reports of exposure to HEPLISAV during pregnancy will be followed to ascertain the outcome of that pregnancy.

In addition, an open label prospective, observational matched cohort study in 5,000 individuals initiating vaccination with HEPLISAV and 15,000 individuals initiating vaccination with a non-HEPLISAV hepatitis B vaccine or secondarily any other vaccine, has been proposed.

The safety evaluation period would be 12 months, and Dynavax proposed that data would be available five years after approval. If necessary, additional cohorts will be followed for refined hypothesis testing. Again, this is an evolving proposal as noted by the presentation earlier today.

I would like to close my presentation with the questions to the committee. Number one, are the immunogenicity data adequate to support the effectiveness of HEPLISAV for the prevention of hepatitis B virus infection in adults 18 through 70 years of age? Please

vote yes or no.

And number two, are the available data adequate to support the safety of HEPLISAV when administered to adults 18 through 70 years of age? Please vote Yes or No.

If yes, is the proposed pharmacovigilance plan adequate to further evaluate the safety of HEPLISAV post-licensure? If no, please discuss what additional studies, both pre- & post-licensure, are needed to further evaluate the safety of HEPLISAV. Thank you.

DR. DAUM: Thank you, Dr. Smith. Dr. Worobec, I see I don’t have to ask you to come up, thank you. So we will have clarifying questions for the FDA presentation first. Dr. Brady?

DR. BRADY: My question is in regard to the autoimmune events that were reported. Was there any indication on past family history of autoimmune disorders because there is some belief that there is genetic predisposition to that.

DR. SMITH: Let me go to slide 31. Is this the analysis you were referring to? I don’t have that answer for all of the individuals. I do know that the individual that had vitiligo, his brother has a history of vitiligo. As far as other reported family history, I do have slides on each of these individuals and could potentially look

through there. But none of them are sticking out as what was reported.

DR. MC INNES: I have a question, most likely for the company. I would like to understand the inclusion and exclusion criteria, and what exactly is solicited in terms of pre-existing autoimmune disorders. This report of 30 subjects who were inadvertently enrolled, I would just like to understand what screening you went through, and inclusion and exclusion.

DR. DAUM: I think I would like to see if FDA folks know anything about this first. Seeking clarifying comments on their presentation, and then if not, we will ask the sponsor.

DR. SMITH: Please correct me. I don’t want to speak for Dynavax, but I know in most of the studies if there was a history of autoimmune disease, if there was steroid therapy for longer than I believe three days, if you had consecutive steroid therapy longer than three days within the last one month, I believe, prior to enrollment, then individuals were excluded. And I believe the rest was a history of autoimmune disease.

And then there was the screening questionnaire in question 16 that went a little more in depth into the patient’s history, correct? But please, if there is

something that I missed, please feel free to --

DR. DAUM: Would Dr. Martin or Poland wish to comment on this question?

DR. MARTIN: Thank you. Just to briefly discuss the reason that these patients came in was typically because they did not recall an autoimmune disease at study entry, and then they recalled something like hypothyroidism or psoriasis as the most common sorts of events that were included in this population that had pre-existing events of special interest.

DR. DAUM: Dr. McInnes, a follow up? And then I have two more people lined up.

DR. MC INNES: I would like to know, did you specifically solicit answers to subparts? How was the question asked, is what I am trying to understand, in soliciting pre-existing autoimmune diseases? As in, have you ever have any? Do you have a family history? Do you, specifically, have thyroid, listing conditions? What detail was asked of subjects?

DR. DAUM: We are seeking FDA presentation clarifications, and I will ask if they want to respond. And if not, I would like to hear the sponsors' response. I sounds like they pass. So you are up.

DR. MARTIN: As an example of what we asked, we

have a questionnaire that we used, that we administered. It is a rather long set of slides, but I could run through it if you would like. The bottom line is, when we took the history from the subjects when they came into the study, they were asked what is their medical history and they gave a long list of items.

In study 16 the questionnaire was designed on the American College of Rheumatology classification criteria, and it asked specific things like have you had joint pain, have you had nodules under the skin, have you ever been tested for rheumatoid factor, and these very specific questions that are part of the classification criteria.

So the diagnosis of someone who had an event of special interest was made based on history alone. And if they reported history subsequent to trial participation that wasn't reported, but that did hit the criteria for an event of special interest. That is this group we call pre-existing events of special interest.

DR. DAUM: Dr. Hudgens, please?

DR. HUDGENS: I had two questions. My first was for Dr. Smith, on slide 64. I was seeking clarification of the pharmacovigilance plan in this matched cohort study. Earlier this morning Dr. Martin referred to this as a two-armed case control study. Would you refer to this as a

case control study? Or is this a cohort study? To me this is not just semantics. A case control study means something very different than a cohort study.

DR. SMITH: I think part of the issue is that this is an evolving proposal, and that this actually represents something that we recently received. But I think Dr. Martin presented perhaps the same, similar thing in much more detail in perhaps even more recent updates.

So I would defer to Dr. Martin or other members of Dynavax, because the information as the clinical reviewer, not as a member of epidemiology but as a clinical reviewer, seems a little bit more updated this morning than what I have received and presented her. I don’t know. Would you like to clarify a little bit?

DR. DAUM: Go ahead if you would like to.

DR. MARTIN: We have been in extended discussions with the Northern California Kaiser group about this study, and we are planning to use their standard design, which is to enroll subjects in the HEPLISAV arm based on people within their systems that receive our vaccine, that then matched with three individuals for a match based on, say, age, gender, and medical utilization over the past year. And that cohort is followed.

So it is a cohort study, but each HEPLISAV

subgroup will have three matched people selected for the other cohort. And they have to have the same, at least one year of claims database or claims history in the database.

DR. HUDGENS: Could you clarify, again, what the sample size will be? Is it 5,000? Or is it going to be 30,000?

DR. MARTIN: Our proposal is that the initial analysis should take place at 5,000. There are roughly 5,000 people in the database today. So looking again when 5,000 are in would be a good interim, to us a good time point for an interim look.

We are prepared to enroll up to 30,000 people in the entire database, and Kaiser Northern California projects that they can do that within three years at a rate of 10,000 per year. Now as Dr. Smith said, this is an active conversation. We are looking, can we add other groups to increase the enrollment rate, and so on and so on. But right now that is what we can commit to, 30,000 people, which will take us an estimate of three years to enroll within Kaiser Northern California.

DR. DAUM: Did you have one other question?

DR. HUDGENS: I do have one other question. This is for Dr. Worobec. Included in the handout were a few bonus slides. I was wondering if you would comment on

slide 45, which shows the comparator vaccine having much higher SPR according to the label than was seen in these studies.

DR. WOROBEC: This probably should not have gone out. The problem with it is, different assays were used which could account for the differences in SPR rates. When we had our internal discussions, trying to figure out where things are at, I tried to put this together as a sort of summary of what we have out there for this study, and what do we know about ENGERIX-B.

If you look at the ENGERIX-B label, the seroprotection rate at week 28 is a lot higher than what we see in studies 10 and 16. And I don’t have an explanation. This is something that we have struggled with. The same for TWINRIX. And in the TWINRIX label they also compared HAVRIX and ENGERIX-B separately, because they wanted to see if there was an interference effect.

So for all these cases, you see it is 92, 95, 96 percent, but in the combined, the modified intent to treat pools analysis. For ENGERIX-B it was 77 percent. It’s at the bottom of the slide, but I will just bring up that the seroprotection rate was determined using a more -- it is sort of the state of the art for now. It is the Ortho Vitros ECi Chemiluminescence Assay. And SPR was determined

using a different kind of an assay, the Abbott's AxSYM AUSAB assay, which is a microparticle enzyme immunoassay back when these other vaccines were approved.

So I think there is that discrepancy. The other issue of course could be the ages of subjects enrolled. For study 16 we had an older population, which might account somewhat for that. But we don't have a good explanation for this. In fact, I may bring this up, if Dynavax would like to comment on these data, if they have any insights.

DR. DAUM: The next question is -- thank you very much -- Dr. Marcuse, then Dr. Bennink.

DR. MARCUSE: I have some. I would like to better understand how the judgments were made about whether the autoimmune adverse events were related or not related to treatment. I think there might be a discrepancy between slide 58 of the manufacturer, in which the vitiligo case is noted on the manufacturer's presentation as a related, and yet on the FDA presentation I think it is noted as unrelated. And so I would like to know a little bit more about how that decision was judged. That is slide 31.

DR. DAUM: Great, and if you don't get a satisfying answer you can bring it up again this afternoon. But I would like to give FDA a chance to respond now.

DR. SMITH: I think part of the reason for that discrepancy is -- I don’t know if you can pull up slide 31 of my presentation -- so I don’t want to put words in Dynavax’s mouth, but I am assuming they were referring to the assessment by the actual study investigator, which was that it was possibly related.

If you will notice, that is the fifth column over. But the SEAC actually determined it to be not related, so our final assessment was based on what the SEAC determined.

DR. DAUM: And of course you could have yet another opinion. Can we move on? Dr. Bennink is next, then Dr. Gellin.

DR. BENNINK: Yes, I want to look at the immunogenicity data from the FDA here. The two slides that I want to look at and compare are slide 17 and slide 27. This is the first presentation, immunogenicity. And if one looks at the week 28 data -- and I know that all of these values are high enough and they are above the titers. But the titers are significantly different between the two studies.

Here you are in the 300s, and in the other study, on 27, the HBV 16, is in 88 to 232. They are significantly lower in terms of this. What really explains that?

DR. WOROBEC: That is a good pick-up. We don't have an explanation. We thought maybe there were differences in the assays. They were done by commercial assay. We don't have that to account for it. The only thing I can think of is, again, in 16 older subjects were enrolled. But it is considerably different.

DR. BENNINK: But was it not statistical? You made the comment, when you were talking about the 16, that there were not age differences within that study. Is that just because they weren't statistical?

DR. WOROBEC: No, the data was quite tight. They were not statistical. We don't have an explanation. It is what it is. And I think it is something for this afternoon's discussion.

DR. DAUM: Yes, but it is a good clarifying question, to make sure that they were as presented. Dr. Gellin is next.

DR. GELLIN: Two related to safety. There are varying lengths of follow-up in the different studies. So I would be interested to know how these -- is it FDA guidance or how these were determined. And then related to that, and I think Dr. Martin had a long list in one of his slides about this category now called AESI, and I am curious if that is a well-defined category with the many

things in small font that are included in that, and if you have guidance on how best these are followed. There are a number of blood tests done at various times, which we can talk about later. But just sort of the general guidance as provided on how a sponsor who is bringing an adjuvant is to assess things going on.

DR. SMITH: After the initial events in study 10 with the two cases of ANCA positive vasculitis, we had input into the following study, study 16, which had the longer safety follow-up period. But as far as the ANA in the anti-double stranded DNAs, those were proposed from the beginning in the trials.

As far as if there is any guidance relative to the AESIs -- is that what you are asking? Any official guidance?

DR. GELLIN: I guess the first thing, is that a defined category going forward?

DR. SMITH: Adverse events of special interest? Yes. There are other trials in which a similar list is used.

DR. GELLIN: And then the guidance on how those are -- because there are many things in those. There is the general guidance on what a sponsor is supposed to do to track those along the way.

DR. SMITH: Does anyone else have an answer to that?

DR. SUN: I just want to make a clarification on the duration of follow-up that Dr. Gellin has asked. Bear in mind that the first study was not conducted under IND. Typically for adjuvant studies, especially new adjuvants, we request that the safety follow-up be one year. And so the second one, indeed, does have that duration of follow-up.

DR. DAUM: Sort of on the same subject, is a question for FDA presenters. Is your analysis complete? Some of the things I noticed were ongoing. Are you still analyzing data that are coming in? Or are you sort of done?

DR. SMITH: We are very close to being done, but probably not 100 percent. There are still some outstanding information requests that we have. Is that question pertaining to one of the particular analyses or just a general question?

DR. DAUM: It is a general question.

DR. SMITH: I would say it is very close to being done. However, obviously this is occurring relatively early in the review cycle. So there still is some outstanding information.

DR. DAUM: I would presume that what is not done is safety follow-ups. Can you give us some idea whether you are weeks, months, or years from being done?

DR. SMITH: Hopefully not years.

DR. GRUBER: I don’t think that we will share that information. I think we have to say that we are of course doing our review within the prescribed timelines, PDUFA timelines. But Lorie, it is fair to say that the clinical review regarding safety follow-ups is still ongoing. However, of course, we have certain PDUFA mandated timelines in which we are supposed to complete a review. But this is not close to being wrapped up.

DR. DAUM: Not close to being wrapped up?

DR. GRUBER: It is not.

DR. DAUM: Thank you for that clarification. We are going to take two more questions and then we are going to have to move on. We can return to any topic the committee likes this afternoon. So we have Dr. McInnes and Dr. Piedra.

DR. MCINNES: I am curious from the product development perspective why study number 10 was not under IND.

DR. DAUM: This is a clarifying FDA session so we will ask FDA to answer. But sponsor may comment if they

wish after FDA is done.

DR. WOROBEC: I think the only thing I can think of is that the study was done in Canada and Europe. They had other studies ongoing. How we found out about study 10 was that this case of Wegener's occurred in that study. And then when that occurred we got the safety report and that is how we knew about the study. But we actually were, it was ongoing in Europe and Canada.

DR. DAUM: Does the sponsor care to comment briefly?

DR. MARTIN: Study 10 was proposed to be conducted in the United States and the FDA asked us to conduct a Phase 2 study, which is study 14 in the US subjects, because we had no prior data. And then we could enroll study 10 in the United States. Study 14 took so much time, that by the time it was complete study 10 was completely enrolled.

So it is true this study was not conducted under IND, but a discussion with the FDA took place regarding study 10 prior to its initiation.

DR. DAUM: Dr. Piedra?

DR. PIEDRA: This might be more of a hypothetical question, but in the pharmacovigilance, when it is done, and the relative risk for hypothyroidism, let's say, it's

two and it is significant, then what occurs? What occurs with regard to the product, and with regard to oversight?

DR. DAUM: My first reaction to that question is that that is for us to advise and for FDA to decide. It is a great question. But I think we will allow FDA to answer a clarifying question based on their presentation, if they can.

DR. SMITH: Do you want me to respond?

DR. DAUM: Yes, please.

DR. SMITH: I would actually defer that question to someone from the division or the office level.

DR. DAUM: Dr. Sun?

DR. SUN: Would you please repeat that question?

DR. PIEDRA: For hypothyroidism, let’s say, in the Phase 4, one has a relative risk of two. Right now it is about 1.8, but it is not significant. But with greater data points it becomes significant during the Phase 4 evaluation. So then my question would be, what happens next? With regard to this type of vaccine, what is the process that would be initiated for the review, and so forth?

DR. SUN: First of all, hypothyroidism is a relatively common disease in adults. I think from the Framingham study, the case rate varies by sex. There is a

predominance of women. The incidence rate is about four per 1,000 per year. So we are dealing with a very common disease. As far as if there were a signal, a safety signal, what we would do normally would be during the review process there would be a discussion with the sponsor along with our division of epidemiology colleagues, with the identify signal to discuss the appropriate study of appropriate size, post-marketing, to get at that issue. And we would build that into the post-marketing pharmacovigilance plan. But that is kind of the process that we go through.

DR. DAUM: I think we need to break. It is an airplane day. There are limited number of places to buy lunch here. We are going to do a 45 minute lunch. We are going to convene again at 12:20 sharp to continue committee deliberations. Thank you. Open public hearing. (Housekeeping details)

(Recess for lunch)

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

Agenda Item: Open Public Hearing

DR. DAUM: As is our custom at this meeting, we have an open public hearing. We will now turn the floor over to Mr. Jehn, who will make an announcement relative to the open public hearing.

MR. JEHN: Hello. As part of the FDA advisory committee meeting procedure, we are required to hold an open public hearing. For those members of the public who are not on the agenda, I would like to make a statement concerning matters pending before this meeting.

We have received one request in advance to speak during these proceedings, and it is going to be Ms. Maureen Kamischke from the Hepatitis B Foundation. We are giving her six minutes to present. Ms. Kamischke?

DR. DAUM: Ms. Kamischke, before you start I have to read a verbatim statement. Would you excuse me one moment? Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes it is important to understand the context of an individual’s presentation. For this reason, FDA encourages

you, the Open Public Hearing speaker, at the beginning of your written or oral presentation to advise the committee of any financial relationship that you have with the sponsor, its product, and if known its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. That is the end of the statement. Ms. Kamischke, you are welcome to address us. Thank you for coming.

MS. KAMISCHKE: Thank you very much. Good afternoon. My name is Maureen Kamischke and I am the Social Media Manager for the Hepatitis B Foundation. I am also the parent of a teenage daughter with hepatitis B, so I believe hepatitis B prevention is critical and it is a personal mission for me.

Had my daughter received the hepatitis B vaccine at birth, she would have avoided becoming chronically infected and saved herself from innumerable trips to the

lab, two liver biopsies, treatment with interferon at the age of 10 months, antiviral treatment and a lifetime of monitoring and living with the threat of HCC constantly looming over her.

But my daughter is not alone. There are more than 350 million people suffering from chronic hepatitis B around the world. Working at the Hepatitis B Foundation, I communicate daily with people who are living with or are affected by hepatitis B. Listen to their stories, and you feel the global burden of this disease. Prevention is critical.

I would like to thank the FDA for the opportunity to make a public comment about the importance of hepatitis B prevention. I am speaking on behalf of the Hepatitis B Foundation, which is the only national nonprofit research and disease advocacy organization solely dedicated to hepatitis B.

Our mission is to find a cure for hepatitis B and improve the lives of those affected worldwide through the research, education and patient advocacy. Dr. Baruch S. Blumberg, who won the Nobel Prize for medicine for his discovery of the hepatitis B virus was one of the co-founders of the Hepatitis B Foundation and was actively involved until his death in April 2011.

The Hepatitis B Foundation and I offer this public statement on our own initiative and at our own expense. We have not received any funds or support from Dynavax, the maker of the new hepatitis B vaccine under consideration.

Briefly, about the Hepatitis B Foundation, the Foundation was founded in 1991 by two couples that responded to a family devastated by the consequences of hepatitis B. Due to the lack of awareness about the seriousness of the disease and the availability of a vaccine, this family now suffers from the consequences of a chronic hepatitis B infection. We are therefore strongly committed to promoting the prevention and control of hepatitis B to reduce unnecessary illness and death caused by this deadly virus.

The Hepatitis B Foundation has achieved a tremendous amount over the last 20 years. At our research facility we support one of the largest concentrations of scientists working on the problem of hepatitis B. We provide a comprehensive outreach program that includes a website with almost 1 million visitors from 180 countries each year.

We lead a public health campaign to increase hepatitis B screening and vaccination in Philadelphia, a

program that has been funded by the CDC as one of two demonstration sites in the country and we are the leading patient advocacy voice in Washington, DC and helped write the viral hepatitis and liver cancer bill that was introduced in both chambers of Congress in 2011.

The need for hepatitis B vaccination is great. The World Health Organization estimates that worldwide, there continue to be 1 million new hepatitis B infections each year despite the availability of a vaccine, and more than 350 million people suffering from chronic hepatitis B. In the US there are still 40,000 new hepatitis B infections each year, and up to 2 million Americans chronically infected with this virus.

The good news is that hepatitis B is preventable, and the current vaccines are excellent and have prevented millions of deaths over the past decades. The medical, scientific and public health communities all agree that the hepatitis B vaccine is life saving.

The hepatitis B vaccine is also the first anti-cancer vaccine approved by the FDA. The 20-year vaccination studies from Taiwan show clearly the hepatitis B vaccination has dramatically reduced the incidence of liver cancer in their country. Despite two very good vaccines that have been approved, there are significant

limitations.

The current vaccines are not effective in many subsets of people such as diabetics and persons undergoing kidney dialysis. These groups represent about 5 percent of the population who are nonresponders and remain at risk for infection. The current vaccine requires three doses over a six-month period. More than 30 to 50 percent of the time, adults do not complete the vaccine series.

The new vaccine, HEPLISAV, that is under consideration today, we understand from published literature will be effective in nonresponders and after two doses. The Hepatitis B Foundation is excited about a new hepatitis B vaccine since there has not been a new vaccine approved for over 25 years.

With the new ACIP recommendation that all adult diabetics be vaccinated against hepatitis B, there is a tremendous need for a new vaccine that is effective in individuals who do not respond to the currently available vaccines. In addition, a hepatitis B vaccine that can be given in two doses should certainly help in improving the rates of vaccine completion among adults.

In conclusion, the Hepatitis B Foundation is not offering an expert evaluation of HEPLISAV, but rather is relying upon published information as the basis of our hope

for the gaps this new vaccine could address. We want to state publicly that there is a need for a new hepatitis B vaccine that can make a contribution to the protection of everyone who is at risk of infection.

Hepatitis B is the world's most serious, common liver infection. But hepatitis B is also vaccine preventable. There is absolutely no reason for any child or adult to be infected with hepatitis B and potentially suffer from end stage liver disease and/or liver cancer. The new vaccine being considered by the FDA today goes a long way in adding the arsenal of preventive tools in making sure all people can be protected from the hepatitis B virus.

Thank you again to the FDA for giving the Hepatitis B Foundation and me the opportunity to speak on the importance of preventing hepatitis B in order to reduce the tremendous disease burden and the number of premature and unnecessary deaths associated with this serious liver disease.

Thank you. I did leave some of our most recent -- our newsletter, and I did have pictures to share but it is too large a room. This is my daughter at 18 months on her second liver biopsy, here at Johns Hopkins receiving her second liver biopsy after she was a non-responder to

interferon. And this is Bailey at the age of 18 months. She did two courses of interferon and was very seriously ill due to chronic hepatitis B. Thank you.

DR. DAUM: Thank you, Ms. Kamischke. We appreciate the comment. Committee, back to business. Is there anyone else who wishes to make a comment during this open public hearing section? I don't see anyone milling around the microphone and therefore I am going to ask the committee to return to its agenda.

Agenda Item: Committee Discussion and Vote

DR. DAUM: We are going to end at 2:30 today, which means we have two hours, and we have two questions. The first question is shown on this slide, and the second question is similar but deals with safety and has some discussion points, depending on whether the committee's pleasure is yes or no. Did you want to say something?

DR. GRUBER: Yes. I am Marion Gruber. I would like to make a comment regarding question two. Question two, the first bullet which speaks to the proposed pharmacovigilance plan and asks the committee if that plan is adequate to further evaluate the safety of HEPLISAV post-licensure?

As you have heard this morning, the applicant has proposed a revised study, post-marketing study. So in

other words we really haven't had a chance to really review and consider and discuss that revised plan within the FDA. So we feel it is really not adequate to ask you now to comment on the adequacy of the proposed pharmacovigilance plans, something that we have not had a chance to review.

So what I would like to ask the committee today is really give us your initial feedback on the proposal as you have heard the applicant stating it this morning.

DR. DAUM: Do you mean the proposal for the pharmacovigilance or the proposal about the adequacy of the safety?

DR. GRUBER: No, not the adequacy of the safety. The question two, are the available data adequate to support the safety of HEPLISAV when administered to adults 18 through 70 years of age. That question stands. There we are asking on the adequacy of the pre-licensure safety database that you have heard discussed this morning.

But of course you also heard the discussion of the pharmacovigilance plan. And as Dr. Smith stated, this was further revised and as the sponsor stated they have further revised the pharmacovigilance plan. So we feel we cannot ask you to comment on this plan absent an FDA conservation review thereof.

But you have heard the sponsor's proposal. So if

you can give us your thoughts about that, that would be good.

DR. DAUM: Thank you very much, Marion. That clarification really helps. What I would like to do is to ask the committee to just raise whatever points they would like for a sort of free-floating conversation for awhile. And then when people start to make the same point over again, and we are milling around aimlessly, we will focus on the questions. And remember we have two voting questions today.

So I recognize everybody in turn, and Dr. Wharton, I am glad you are starting off.

DR. WHARTON: Thank you. I have my questions for Dr. Gruber. For question two, my assumption on looking at this question is that we are being asked to evaluate the adequacy of the safety data for use in the general adult population 18 to 70 years of age, not in high risk populations but the general adult population.

DR. GRUBER: That is correct.

DR. DAUM: Dr. Marcuse, start us off.

DR. MARCUSE: Earlier today there was a comment in response to a question about the period of observation that the FDA requires when a novel adjuvant is being introduced. And there was reference made to a year follow

up. I would like to understand better the basis for that. Here we have a new adjuvant. We have about 2,000 patients that were followed for one year. Is there any kind of guidance or past experience around that?

DR. SUN: This is Wellington Sun. Let me try to answer that question. First of all, I think we are talking about the investigational phase of vaccines. So these are vaccines that are investigational or with an investigational adjuvant. We typically -- and I don’t know if I would call it a requirement, but we typically suggest and strongly suggest to the sponsors that in clinical trials involving these products, to have safety follow up for a year.

Why is that? The reason we believe is that we are trying to err on the safe side, and being very conservative, understanding that potentially autoimmune diseases can manifest itself over the course of a long period of time, and that the pathophysiology is such that it is an insidious, and I think Dr. Smith referred to it in her slides as it could be an insidious process where it takes time to diagnose.

So we figure that a year’s time is a reasonable timeframe for that to occur.

DR. MURPHY: I would like to follow up with Dr.

Gruber, with Melinda Wharton's question. She asked about the general adult population. Clearly there are high risk adults who don't necessarily identify themselves, and would be considered part of the general adult population. So please clarify what is the status for high risk populations in the answer to your question.

DR. GRUBER: The indication states HEPLISAV is going to be indicated for the prevention of hepatitis B virus infection in adults age 18 through 70 years of age. Granted, there may be some high risk population included in this general population. But the point that we wanted to make is that the studies that you have heard about this morning, 10 and 16, they really were not powered to look at the efficacy, if you want, of this vaccine in these high risk subpopulations that were mentioned this morning.

So we really, this is the general population 18 to 70 years of age, and that is what we ask you to elaborate on. But we haven't seen any analysis that was powered to really make specific statements regarding the immunogenicity in these subpopulations. The analyses conducted were descriptive, they were exploratory. But they were not really done prospectively with adequate power to really even consider an indication at this point for these type of subjects.

DR. MURPHY: Would you then envision that it would require a separate indication for each high risk population?

DR. GRUBER: Not each high risk population. It depends on how do you define it. I think there could be the potential for a separate indication for certain subject populations that are at high risk. I cannot tell you that every high risk population would have to be studied separately. So if I can have a minute, I would like to confer with my colleagues a little bit. Is that okay?

DR. DAUM: Of course it is okay. Can we go on?

DR. GRUBER: Yes, you can go on.

DR. DAUM: I would like to ask the company -- I have noted you want the floor -- I would like to ask the company what their plans are with respect to this issue. Because we heard that a few patients got in with underlying disease, but most patients were excluded. And I think that Dr. Murphy is correctly raising the point of how are you going to deal with this, if licensure was offered. Particularly with a new adjuvant.

DR. MARTIN: Dr. Murphy, do I understand your question right about high risk populations who are high risk for hepatitis B infection? So all of the current vaccines are indicated for use in adults? There is no

specific indication for use in these high risk populations. The ACIP is the group that recommends that one particular group or another are at high risk and should specifically be used or specifically be vaccinated.

That is our intention that we are trying to come to here. The purpose of today's presentation is to say that for those high risk populations who are immunocompetent, that is, normal biology individuals, not the CKD population, not the HIV population, not the CLD population, which is why we call them out as separate populations, that is the population that one should be thinking about in the context of our application today.

DR. DAUM: On the same subject, would you exclude pregnant people from that?

DR. MARTIN: Yes. Our recommendation is that, or our proposal that we propose to the FDA is that this be a category B product if needed. But the safety and immunogenicity has not been established in pregnant women.

DR. DAUM: So women would need a pregnancy test if they are adults?

DR. MARTIN: The way that we have conducted the trials was that we did require a pregnancy test. And we don't have data other than the 19 events that I showed you for what occurs with pregnancy and exposure to HEPLISAV.

DR. BRADY: My question goes back to the adjuvant. It would probably be addressed by the FDA. Do we have any data from toll-like receptor for use in CERVARIX as far as safety that we might be able to use? Since that wasn't an initial adjuvant. That was added in order to -- I know it is a different toll-like receptor that this works on, but that would potentially have longer safety data.

DR. DAUM: Dr. Gruber, you are ready. You will e next.

DR. MARTIN: Dr. Brady, there is more data with CERVARIX vaccine and the TLR4 adjuvant. In fact, the same group that we are talking to about conducting our post-marketing study has recently published in vaccine the results of their long-term pharmacovigilance study post-marketing for CERVARIX. And no important signals were identified in that study.

DR. BRADY: Was that including the autoimmune --

DR. MARTIN: Yes, it was. And in regard to a question that was asked earlier about these adverse events of special interest, I will just make the point that our list is identical to the list that was reviewed yesterday in the context of that adjuvanted vaccine.

DR. DAUM: Thank you. I want to see if Dr.

Gruber is ready to speak again.

DR. GRUBER: Yes. We had some further internal deliberations. To clarify, subjects at high risk that fall within the age range of 18 through 70 years of age would be included and could receive the vaccine. So if you look at smokers, obese subjects, however, the difference is -- and that is what I want to try to say -- in order to get specific indication that this vaccine prevents hepatitis B in obese patients or diabetics or end-stage renal disease, that would require specific studies with specific endpoints.

But there is a whole range of these high risk persons that could fall in this age range, and that would not exclude -- we would not exclude these persons from receiving the vaccine because they fall under this age range.

DR. BENNINK: I have a series of questions I want to ask the company, from this sense. First, in terms of this, what is the biological half life of the adjuvant? And in some of the early studies what was the kinetics for example of granulocyte activation or infiltration after adjuvant injection? Or how long did this last, or anything along that line? Do you have any information about that?

DR. MARTIN: Yes. First, let’s start with the

duration. We measured the pharmacokinetics of 1018 in the plasma. I have been doing it with chronic kidney disease following injection with HEPLISAV. And the half life is on the order of four hours in the serum.

Most of the adjuvant and the antigen is maintained at the injection site. There is little systemic exposure. But what is there goes away within four hours. Could I have the interferon alpha inducible gene slides, please? We have studied 1018 in the context as a single stand-alone therapeutic agent early in its development for oncology.

And we studied patients with non-Hodgkin's lymphoma in that context. We collected PBMCs from patients with non-Hodgkin's lymphoma and measured interferon alpha inducible gene expression in the PBMCs from those populations. And in that setting the exposure was to HEPLISAV doses, or to 1018 doses, 12 times higher than that. In HEPLISAV we see high levels of interferon alpha inducible genes.

But at the day 13 sample, which is now seven days after the six-day dose, that expression has gone down to zero. So at the expression level, the effect of 1018 is gone by seven days, and it peaks at 24 hours. Then you had a question about the injection site?

DR. BENNINK: Yes, simply I wanted to know how much activation of granulocytes or the neutrophil infiltration or other things like that.

DR. MARTIN: I am not able to answer the question about neutrophil invasion. What I can say is that 1018 and the antigen have to be injected at the same site. If you, for instance, inject a mouse in the leg and the tail, you don't get an adjuvant effect. It has to be co-administered in the leg.

DR. BENNINK: I guess why I was asking some of these questions is trying to see if there was any aspects of kinetics of these things that then could even potentially answer any of the side effects that one has seen, or anything along that line. I guess it is in those terms. Let me ask a couple of the questions. So the question that we ask the FDA earlier in terms of the difference in the data between the two studies in terms of the geometric mean, do you have any comments on that?

DR. MARTIN: Yes. I think it is very straightforward, what is the explanation for that result. And it simply has to do with the age group between the two studies. In one study the subjects were 40 to 70. In the other they were 18 to 55. Can I have the SPR by age group slide, please?

And this also gets back to another question that was asked about why is the SPR in our studies -- SPR by age group, please, by age subpopulation -- the question was asked why are the SPRs in the HEPLISAV program substantially different from those that are seen in the label? And again it is because of disparity in age enrollment.

Seventy-five percent of our subjects were over the age of 40. When we look at the results by decade, SPR by decade, we see that in the young adults the SPR that is in the 18 to 30 year old age group, the SPR was 93 percent, which is completely compatible with the package inserts and reported literature for this particular age group.

It is in the older subjects that you see that the ENGERIX-B SPR declines. And again, this has been reported by many other sources than ourselves. The best source, the largest source was a study conducted by Averof(?) that was conducted at the CDC, a publicly funded study. And in that study they showed this same decline in SPR that really had an onset after the age of 40. And that was seen for both vaccines. So it is clearly an age effect.

DR. BENNINK: Another question, as I keep going here. Bruce asked a question earlier about doses after a failure to respond. But I think there was a -- the slide

that you showed, if I am correct, was using the drug after a first immunization with one or the other. But has it ever seen where you have done three doses of the GSK drug and then had a failure, and then used yours and saw if you could get a response?

DR. MARTIN: In the results that I showed you earlier from study two, those were subjects who had failed a complete regimen with one of the currently licensed vaccines, either RECOMBIVAX or ENGERIX in their own clinical setting. And that is what made them eligible to come into this trial. And they got a single dose of vaccine in the context of our trial.

So these were health care workers and other first responders who were vaccinated, had their serology tested as per the typical protocol, and found to be nonresponders.

DR. BENNINK: And on your slide 42, along the same line in terms of doses, there were three doses. It looks like you had 5.7 percent or something that was given a third dose of HEPLISAV.

DR. MARTIN: Yes, in some of our earlier trials, particularly for older subjects, we gave a three-dose schedule because in the early development we weren’t sure if the most immunosenescent population would get a good response to two doses. So we have a study where we gave

adults age 40 to 70 three doses of HEPLISAV.

DR. BENNINK: And did that improve it?

DR. MARTIN: Can we have the SPR by visit for study four please? And then be prepared for GMC in study four? The SPR in subjects at month six prior to receipt of their third dose of HEPLISAV was 98.5 percent. Following the third dose, the SPR proceeded to hit 100 percent. This is in a trial, 200 people per group, that was conducted in Asia with a different hepatitis B service engine subtype.

This is ADR instead of ADW2, the subtype that is used in the United States. It was the results of this study that showed to us that we did not need the third dose of vaccine. We get very high levels of protection in an older population with two doses of vaccine. So the two-dose schedule was moved to.

Now when we look at GMC in this population we do see a response to that third dose. And with the GMC level you do get a boost from the third dose. But for SPR, we had high SPRs without it, and so we moved forward to develop the product as a two-dose schedule.

DR. BENNINK: And one final, at this moment, to try, and that is that in your studies and everything you have been excluding people that had titers to hepatitis B. Has the drug been given to any patients diagnosed with

hepatitis B? And if so, was there positive effects in terms of the hepatitis? Or were there negative effects, if that happened?

DR. MARTIN: You mean as a therapeutic vaccine?

DR. BENNINK: As a therapeutic, but just in fact if you start giving this to the population you are not going to be testing everyone to have negative titers to it. Is there any adverse effects from that, or any positive effects?

DR. MARTIN: We did not see any adverse effects. But what we did see is in those subjects who had an antibody concentration, say, above five but below 10, that they tended -- so in fact they met the criteria for eligibility, but in fact they probably had been pre-exposed. We saw very high titers, which would suggest an anamnestic response in that population. That was true for both vaccines, very high titers in the relatively high pre sample.

DR. DAUM: Do you have the data?

DR. MARTIN: Do we have it, Dr. Janssen? Thank you. We will get it shortly. Dr. Daum will get it for you shortly.

DR. DAUM: I have Dr. Cheung and Dr. Marcuse. But before I call on them I would like to give fair warning

to committee members that I really want to hear from everybody. So that if after awhile there in the conversation, if everyone hasn't spoken, they will be called on. Dr. Cheung?

DR. CHEUNG: This is for the sponsor. There seem to be two subpopulation groups that are susceptible to hepatitis B. One is those with renal failure. The other is in the Asian population a lot of those are through congenital transmission from mother to child. Do you have any data on those two groups?

DR. MARTIN: Can we have study four back up, please? We don't have very many Asians who participated in the Phase 3 trials. It was a rather small number. I will show you the data from that. But the study four that I just showed you where we looked at three doses of HEPLISAV, this was a trial that was conducted in southern Asia .

So it is specifically in Korea, the Philippines and Singapore. And so all the subjects in this trial were Asian subjects. And you see that the treatment effect between HEPLISAV and ENGERIX-B is the same, albeit with a different sub-unit.

In the context of our pivotal trials, that is, trials 10 and 16, can we have the racial subpopulation data please? In that study, the SPR, as was shared by the FDA

colleagues this morning, was consistent across groups. But the small number of subjects precluded a finding of statistical significance.

In particular, the Asian populations tended to be young, and you see their response to ENGERIX-B is higher than we saw in the rest of the population. So these subpopulations would have, quote, met the, quote, criteria for non-inferiority. But the Asian population had a high response in the ENGERIX group, the same response in the HEPLISAV group.

DR. DAUM: How old are these people?

DR. MARTIN: The Asian subpopulation primarily comes from study 10, although some were also from study 16. The black population in this study primarily comes from the US trial, which was study 16, which was the older trial. So the black population in this, the black subpopulation, tends to be older. The Asian subpopulation tends to be younger. And the white population, which was the predominant population in both studies, tends to look like the overall result.

DR. CHEUNG: What about patients with renal failure? Anything in that group?

DR. MARTIN: Can we have study 17 SPR by visit please? We have conducted a pivotal trial, but to repeat,

this is not part of the application. The data had been submitted to the FDA but not in the context of this BLA. So I want to be clear about that.

In that study we have evaluated three doses of HEPLISAV at zero, four, and 24 weeks, compared to the double dose of ENGERIX-B at zero, four, eight, and 24 weeks. The primary endpoint was week 28. The results of the primary endpoint show that 89 percent of HEPLISAV subjects, or 90 percent of HEPLISAV subjects and 82 percent of ENGERIX-B subjects were seroprotected at the primary endpoint visit. The difference is eight percent.

The lower bound of the 95 percent confidence interval was 1.7 percent. We looked at the higher threshold of 100 because many people find that to be a more interesting number in the context of this population. And again, the difference in SPR was 10 percent with the lower bound being 1.9 percent.

And finally, this is a population where people care about GMCs. So we also have presented the results for geometric mean antibody concentration by visit. And you can see that the HEPLISAV group was higher at week 28, and continued to have an antibody rate of decay similar to the ENGERIX-B group.

We have rolled over this study population into a

follow up study that will last for four years. The farthest advanced subjects are about 18 months into the study at present. But the results of the follow up we presented last week at the American Society of Nephrology meetings, and you can see that the advantage in the HEPLISAV group that was there at the peak has been maintained out to 600 days post the peak. And the slope of decay is the same in both vaccine groups.

DR. MARCUSE: This is a question for the adjuvant experts in the group. There is a lot of experience with aluminum salt adjuvants, and I have always assumed that one aluminum salt adjuvant was rather similar to the other aluminum salt adjuvant in terms of immune response. Now we are dealing with adjuvants that affect toll-like receptors.

Dr. Brady brought up CERVARIX. My question is, to what extent can the experience with a lipid-based adjuvant inform our thinking about the safety of a nucleotide adjuvant? Are those all apples and oranges? Or because they are both toll-like receptor adjuvants, is there some reason to think that one experience would inform the other? I don’t know how to deal with that.

DR. DAUM: I will leave that as an open-ended question for anyone that cares to respond.

DR. BENNINK: I don’t know if I want to respond.

Anna can respond as well here. I don't think you can make a real good comparison between the two, because they are really stimulating the cells differently. So there are some things that may end up to be the same, but I think a lot that are different. So I don't think you can really use them. To me you can't.

DR. GOLDING: I wanted to expand a little bit on what Jack just said. I think that each of those TLR agonists, they have some things in common in terms of the downstream signaling. But they also have some differences. And ultimately, the genes that get activated include both good cytokine and some inflammatory cytokines. And I don't think one can necessarily learn from experience with one TLR agonist to expect what happened with others.

Plus, each of those specific novel adjuvants will undergo certain modifications to optimize for immunogenicity and maybe reduce reactogenicity. So it is also very much important in how each of these TLR agonists is presented. For example, the MPL, which is in CERVARIX, is part of a combined combination adjuvant that then is combined again with the antigen.

So while CPG in the context of the hepatitis B is formulated in a totally different way with the antigen, I think it ultimately will be really important, a lot of the

questions that were asked, for how long, where is it going, is it staying locally or does it go systemically? So what is the level of systemic exposure, and for how long? And are there any changes in the overall immune function, T cell subsets, et cetera?

I really think that each of them does require its own level of deep investigation rather than try to learn from one and expect what the other will do.

DR. DAUM: Dr. Golding, thank you very much for that comment. Dr. Piedra?

DR. PIEDRA: There currently are a number of vaccines that are licensed for adults and the list probably will become bigger. And there are some vaccines that are yearly, like influenza. And so I was wondering if data has been developed, or what are the plans to look at reactogenicity and immunogenicity with concomitant administration, and what should be, if there are issues or if there are not, what are the time periods also that should be looked at between administration of one vaccine versus the other?

DR. MARTIN: Our plans are, following approval, to conduct concomitant use trials with commonly used adult vaccines. So I would include on that list, for instance, pneumococcus, flu, zoster, HAV as sort of for prototypes.

We have not shared with the FDA our specific plans to conduct those trials. So I don’t really want to comment more than that at this point in time.

But clearly one needs to create data that will allow the clinician to understand can they or can they not co-administer these vaccines within the same visit. And in the context of our clinical trials where we are trying to evaluate the immunogenicity of our vaccine on itself, we precluded co-administration of other vaccines around the time of our vaccine.

DR. DAUM: I would submit that this is not a trivial issue. It is pretty hard to get adults in for immunizations. And in a sense what we would be left with is having to give your vaccine with its novel adjuvant separately because we don’t know anything about in combination with other vaccines. I wonder, I view it as a fairly serious omission that that hasn’t been studied so far.

DR. MARTIN: That is why it is very high on our list to do.

DR. DAUM: Okay. Other comments?

DR. MC INNES: I think you said study number four was done in Asia. Is that correct?

DR. MARTIN: That is correct.

DR. MCINNES: Could I just see the numbers again? The number of people in study four?

DR. MARTIN: Yes. There were roughly 400 people, 200 in each age group. It was randomized one to one. We will have the slide back here for you shortly. As I recall, it might have been 205 and 204 in the two age groups, but it is roughly 200 per vaccine group.

DR. DAUM: Going to the same point, with a vaccine with a novel adjuvant, how about the different ethnic populations in the US, particularly the African-American population? I saw pretty few studies, subject studies, in that group.

DR. MARTIN: Yes. Here is the study four results. You can see the ends at the bottom of the slide for the immunogenicity analysis. It was 205 in the HEPLISAV group, 204 in the ENGERIX-B group. Can I have study 16 baseline characteristic please? And then we will follow up with the racial SPR, the SPR by racial group slide, please?

Dr. Daum, the trial 10 was conducted in Canada and Germany and had relatively few non-whites who participated in that study. So you see there were 94 percent in the HEPLISAV group, 92 percent in the ENGERIX-B group that were white, and just a small proportion of

blacks, Asians or others.

In protocol 16 which was conducted predominantly in the United States, the proportion of blacks who participated was much higher, and so the data that I am now about to show you that shows the SPR by group, you can see is dominated for the black population by study 16, which was the older population.

So when we look at the results by racial group for HEPLISAV you can see it is fairly consistent across these populations, also the ends in the Asian and the other group are smaller. In the ENGERIX-B group there is some variability related to the variability of age, with the Asians tending to be younger in the pooled population and the blacks tending to be older in the pooled population.

DR. DAUM: I understand. But you are submitting a licensure application in a country that has a substantial minority population of multiple different kinds. And a new adjuvant, I am just not sure how it performs in these groups, and I am not terribly reassured by these very small numbers.

DR. MARTIN: That is one reason why we think that the study four data is so important, that the treatment effect between the groups is the same and the safety was the same in study four as in the other studies. But again,

it uses a different subtype and therefore the immunogenicity results are not included. The safety results from that population are included in our BLA. But the immunogenicity results are not included from study four.

DR. DAUM: Dr. Gray, would you like to comment on this?

DR. GRAY: I don’t have a lot of questions. I think the data are quite compelling, that we are seeing no evidence of non-inferiority compared to an already approved vaccine. And in many cases, many metrics, better performance. So I think I am ready to vote.

DR. DAUM: Very much. Dr. Tacket, you haven’t said much so far.

DR. TACKET: No, I have not. I am impressed with the fact that the various autoimmune diseases like Wegener’s and Bell’s Palsy and erythema nodosum occur at quite a larger or higher incidence than they do in the general population. And I just wanted to point out that we are comparing this new vaccine to ENGERIX, in which case they are very similar in terms of side effects. But nevertheless they are significant rates compared to those who would not be immunized.

DR. DAUM: Can you take that thought a little

further? Is something missing in your mind?

DR. TACKET: No, but I think when we look at these raw numbers that perhaps if we did not have the experience with ENGERIX for many years that we might feel differently about them. What we are comparing is the new vaccine to ENGERIX.

DR. AIR: I am fine. I do have lots of questions about the assay methods and this measurement of antibodies. And then you tell me that the different assays are giving different results. But the bottom line is, there is a head to head comparison here with a vaccine that is accepted and is very effective. And so I think my concerns are theoretical but not practical.

DR. DAUM: Other committee members care to comment? Dr. Piedra, and then I have a comment if there aren't others.

DR. PIEDRA: My comment, this is just a little bit more for information. Both there is a question about the T cell induction with regards to CPG. I was wondering if there was more information on T Reg, since that seems to be an important T cell in the regulation of inflammation.

DR. MARTIN: We do not have any current data regarding T cell function in patients who have received HEPLISAV. We do have a systems biology grant that has been

funded to Baylor that we are collaborating with, to look at both cellular and genomic responses to surface antigen with 1018 compared to surface antigen with alum in both normal response and hyporesponse of populations.

That will provide some insights into both the T cell biology as well as the transcriptome differences between alum and 1018 in the context of the same antigen. But we don’t have any data that I can share with you today.

DR. DAUM: Dr. Gellin?

DR. GELLIN: Clearly what is novel here is the adjuvant. So that is where a lot of the focus is. Maybe you talked about this, but the dose finding for the adjuvant -- and I guess what I am getting at is, what other experience can we learn about the adjuvant? And was there some issue at -- obviously you are trying to find the optimal dose, but did you find issues with higher doses that might give us some other insights into how it performs?

DR. MARTIN: In the context of our chronic kidney disease studies we did evaluate a double dose. So that is a 40 microgram surface antigen in 6,000 micrograms of 1018 ISS. And while there were no true safety differences between those two groups, the higher concentration was definitely associated with more local and systemic

reactogenicity.

And so we did not pursue that higher dose any further. We have settled on the 20 in 3,000 both for the healthy population as well as that is the dose we evaluated in our CKD program.

DR. DAUM: I guess I should share my overall sense of uncomfortableness with the relatively small number of patients studied in a novel adjuvant. And I can’t tell, and perhaps I can ask Dr. Hudgens to comment on this if he wishes to, but I can’t tell with rare events like this, and relatively small numbers of subjects that have been immunized and some are in varying degrees of follow-up in terms of their study, whether I believe that there is a concern about the toxicity or the safety of the adjuvant or not.

I wonder if you have thought about that, because we are talking about rare events, rare events in studies that have one, two, three, or four thousand subjects may not become apparent in terms of their occurrence or differences. And we have a public perception of perhaps licensing a vaccine that has a new adjuvant in it and then concern about not enough subjects studied to detect rare events.

And I wonder if you would comment on that?

DR. MARTIN: From our perspective there are several important things that need to be considered with regard to that question. The first one is, for instance, if we take a disease like Wegener's granulomatosis, we heard numbers earlier today that the event rate is something like 12 per 1 million. Well it is 12 per 1 million in the general population. It is not 12 per 1 million in subjects 40 to 70 years of age.

So if we make some adjustments for that -- and we can look at the age distribution, where almost every case happens in people who are over the age of 40, so all 12 of those cases will happen in individuals who are over the age of 40. Forty percent of the United States population is over the age of 40. So a more relevant rate to evaluate would be something like 11 per 400,000, not 12 per 1 million.

If we take 11 per 100,000, now the rate in the population that is being studied is one in 36,000. And it is not unusual. It is not expected, but it is not unusual to see a one in 40,000 event occur in a population of 4,000.

Secondly, we need to consider as another point related to something that Dr. Sun said earlier today about the importance of the long follow-up. The long follow-up

is important to detect potential autoimmune signals for novel adjuvants. But we need to keep in mind that the longer we extend the follow-up, the higher the probability we are going to see coincidental events happening in that population over time.

And if I take an older population that has got events like Wegener's granulomatosis, or more common events like hypothyroidism, I am going to see more if I follow people for 12 months than if I followed them for 28 days, which is what we did in the early days of these vaccines in this class.

So there is really an issue around signal detection here. And the most important to go back to even Golding's comments earlier today -- we don't know what the signals are to look for here, which is why the hypothesis has to be all disease, all autoimmune disease, looking for imbalances. And as the samples expand, then you can get into more specific hypothesis testing.

So this initial set, which shows no increased relative risk for all these events that we talked about this morning that we presented to you, seems like an excellent database to say I don't see a signal yet, it is appropriate to expand the testing but with very careful post-marketing pharmacovigilance that could then get me a

log further in my risk exclusion.

That is, get me to a one in 10,000 event rate as opposed to a one in 1,000 event rate, which I get to with 3,000 to 4,000 subjects. Get to 30,000 subjects. And then we have got systems like VAERS and VSD to get us to the one in 100,000 event rate. So that is our proposal here.

We think that is logical drug development, and it is really what is appropriate to continue to be concerned about safety, to carefully measure safety as we roll out this new vaccine. But at the same time get a product out to the public that clearly has immunogenicity advantages over the current products.

DR. MCINNES: I want to state that I am concerned about the demographic distribution in which these data have been collected. I think the Asians are severely underestimated here, under-represented here. And most of the whites are non-Hispanic, so I don’t feel like this is a reflective demographic pool that we are looking at here.

I am not trying to take away anything from the rigor of the conduct of the studies that were done and the data collection. It is just a statement of the demographic data that I see.

DR. DAUM: More comments? Go ahead, Dr. Dubovsky.

DR. DUBOVSKY: Just a follow-up on that, and this

is really a question, is there a scientific reason to believe there would be a racial disparity in their response to CBGs?

DR. DAUM: That is a fair question, but I don’t know if it is a relevant one. We need to have a vaccine that is acceptable for all of our people.

DR. DUBOVSKY: Absolutely. But the notion is if there is a biological plausible reason to go for that, it would be more pressing to answer that question pre-licensure versus post-licensure where you are going to collect that data through the Kaiser system.

DR. MCINNES: I disagree. I think we have a responsibility to collect and see those data in the context of making a decision about licensure for the whole population.

DR. DAUM: Other comments? Dr. Piedra?

DR. PIEDRA: I wonder if you could clarify a little better with the issue of the post-marketing study that is being proposed, and what number of individuals and at what time period would be adequate to assess for uncommon events.

So will 5,000 individuals in one year? Or will it be 30,000 individuals in five years, be adequate to address these types of uncommon events with power?

DR. MARTIN: Let me just briefly discuss the methodology that Kaiser uses. There has been a recent paper that has been published where they looked at live, attenuated influenza vaccine as a very good example of how they typically conduct this method. So the first analysis is conducted with no a priori assumptions about what ICD-9 codes may or may not fall out of the analysis.

So they look at all 5,500 ICD-9 codes and look for disequilibrium in event rates either by time interval within the HEPLISAV, or within the targeted vaccine population, or across cohorts if you are comparing it to the group that gets vaccinated with the control vaccine. So there are two elements of signal detection, all ICD-9 codes are conducted, and then one simply looks for signal, what pops out of the signal.

And it goes back to the idea that we cannot a priori predict which ICD-9 codes might show signal. So it starts off with an unbiased assessment looking at every ICD-9 code. With regard to the duration of follow-up, we have not discussed this with the FDA but it seems to me that the minimum follow-up needs to be one year.

Of course the longer the follow-up goes then the longer it takes to get the complete dataset. And for the statistical reasons that I mentioned about being able to

detect events that occur at a one in 10,000 rate, we think 30,000 observed HEPLISAV recipients is the right number for this study.

DR. DAUM: Other comments? The AV guy will put up the first question, while Dr. Cheung makes his comment. And then we are going to focus on question number one.

DR. CHEUNG: I just want to ask the sponsor about the pharmacovigilance plan. Since at least in the preliminary data you presented there might be some association with thyroid disease as well as some other immune disease, what are your plans in your follow up? When you follow up those patients, what are the parameters that you follow?

DR. MARTIN: The way that they routinely conduct the analysis is, they look at all claims in their health claims database with no a priori hypothesis about what diseases may fall out into equilibrium between either the time intervals within the HEPLISAV group or the cross-cohort comparison.

So it is every IC-9 code is looked at. And as you see disparities then you begin to follow up and focus in on those particular signals. So one could, it would be possible to focus on hypothyroidism from the beginning. We have not discussed that. That is not their standard

methodology. Their standard methodology starts with all ICD-9 codes in the analysis. But we could change that in collaboration with the Northern California Kaiser Group.

DR. DAUM: I think it is time to focus on the first question. I am going to make sure that everybody is focused on it by reading it. Are the immunogenicity data adequate to support the effectiveness of HEPLISAV for the prevention of hepatitis B virus infection in adults 18 through 70 years of age?

I know we have discussed a whole bunch of stuff and there might be very little more discussion to have. Hopefully there is some. And then we will vote on this question. So I would like to focus comments now on immunogenicity data adequate. Dr. Murphy, then Dr. Wharton.

DR. MURPHY: Obviously the immunogenicity data are based on the seroprotection rates, and that has worked for the standard vaccines. But I think we would probably, at least I would like to see some longer term studies that would see how this holds up over time.

DR. DAUM: Thank you, Dr. Murphy. Dr. Wharton?

DR. WHARTON: The immunogenicity data that was provided by the sponsor looks excellent. But I have the same concern Dr. McGinnis does about the demographic

composition of the population. I think what we have looks really, really good, but it is not representative of the United States.

DR. DAUM: Thank you. Other comments about immunogenicity data? Dr. Air?

DR. AIR: It must be here somewhere, but I am missing it. Are you following these people for hepatitis B infection after vaccination?

DR. DAUM: We will ask the sponsor for a response.

DR. MARTIN: We are not.

DR. DAUM: Okay, there you have it. Other comments on immunogenicity? Dr. Dubovsky.

DR. DUBOVSKY: As part of the pharmacovigilance plan, is that an endpoint you envision capturing? The hepatitis B? As part of the pharmacovigilance plan is that one of the parameters you are going to capture, infection of hepatitis?

DR. MARTIN: One would capture those claims in the claims database, yes.

DR. DAUM: Perhaps it is time that we vote on immunogenicity, then. We are going to do this by new electronic way, new to me. It is not new to anyone else, I recognize that.

MR. JEHN: FDA has simultaneous voting. There are three buttons here to choose, the yes, abstain and no.

DR. DAUM: So at this time I will ask each voting member to press the button that best conforms with his or her opinion. And then we will look at the results electronically and ask if anybody wants to comment on how they voted or not.

(Pause for vote)

MR. JEHN: There are 13 votes yes, zero abstained and one no. We will get the breakdown here. For the record, Dr. Gellin is a yes, Dr. Hutchens is a yes, Dr. Air, yes, Dr. Tacket, yes, Dr. Gray, yes, Doctor Cheung, yes, Dr. Murphy, yes, Dr. Bennick, yes, Dr. Piedra, yes, Dr. Marcuse, yes, Dr. Wharton, yes, Dr. McGinnis, yes, Dr. Brady, yes, and Dr. Daum is a no.

DR. DAUM: I guess I should speak and explain myself. I am concerned that there are not enough data and different ethnic groups to be sure that the immunogenetic response is adequate. And I am concerned also about the no data presented about other vaccines that would be given simultaneously. I think those are two important issues. Certainly if this were a pediatric vaccine, we would be extremely jumping up and down about that.

I am jumping up and down about it for an adult

vaccine, because we are all trying to augment adult immunizations. We are giving simultaneous vaccines, like TDAP and flu, to name two, pneumococcus to name a third. I don't see this as a separate visit vaccine, so I think the data are not adequate.

I am also concerned globally, and I don't know much more and I suspect I won't get much more if I press, and FDA statement that they haven't finished analyzing the data yet and so I don't think it is time to say that something is adequate or not adequate based on that. So that is my reason for voting no.

We are ready to move onto question two. Question two concerns safety. And are the available data adequate to support the safety of HEPLISAV when administered to adults 18 years through 70 years of age? First we will vote yes or no, and then depending on what we decide we will have another discussion point as you see below. Let's first have discussion, as you wish, regarding the safety issue. Committee members? If there is no discussion, we can vote. Dr. Wharton and Dr. Marcuse?

DR. WHARTON: First, having a hepatitis B vaccine which is more immunogenic in populations that don't respond optimally to current vaccines is a good thing. I am glad to see this work being done. That said, I don't think the

safety database is sufficiently large to support a recommendation for use in the general adult population given that this vaccine contains a new adjuvant.

DR. DAUM: Dr. Marcuse?

DR. MARCUSE: This is a very exciting vaccine and we need new adjuvants. That said, it comes down to weighting the potential benefits versus the potential risks. We just heard that the post-marketing study size that was desired is 30,000 to detect an event that might be as rare as one in 10,000.

At the present time we have 2,000 patients who have been followed for a year. And if the rule of three applies that allows us to detect rare adverse events that occur at the rate of one in 700. And things that are more rare we don’t have an adequate database for yet. So I end up feeling that since we have vaccines that may not be optimal but that are effective, that is too flimsy a safety base to accept in the general population.

DR. DAUM: Dr. Marcuse, thank you for your comment. Other comments from the committee? We can go ahead and vote if there are not any.

DR. HUDGENS: Could we have some clarification about what happens when a safety signal is detected in the matched cohort study, the proposed matched cohort study of

30,000 HEPLISAV vaccinees versus 15,000 matched controls? What would happen if it was determined that this was causing some adverse events, the type that other committee members are worried about?

DR. MARTIN: Thank you for the question. In a post-marketing context there are basically two forms of pharmacovigilance that will take place. One is spontaneous reporting of events that could happen through VAERS, reported to the sponsor, by either patients or their physicians. Those events get processed on a regular basis, and if there are regulatory communications that need to take place they happen directly between the sponsor and the FDA.

In the context of the specific pharmacovigilance study at the appropriate intervals, and we are proposing that first one be at 5,000, you would cut the data. You would look for disequilibrium, and if one finds it then again there needs to be a regulatory discussion with the FDA about what has been observed.

DR. HUDGENS: I am trying to understand the distinction that my colleagues on the committee here are concerned with. And that is, whether or not this, if this sort of thing is going to happen, whether or not we detect it before or after licensure. Is that the issue at hand?

DR. DAUM: We are looking for your opinion about that. So the question before us is regarding safety. And the concern for you is -- concern is not really the right word. The issue for you is whether you think you know enough about safety right now that you could vote yes, the data are adequate and here the pharmacovigilance that is going to go on after licensure.

Or, do you think there should be more data generated before licensure? I think FDA is seeking your advice on this, and so we would like to hear your opinion about that.

DR. HUDGENS: Everything I have heard so far from a statistical standpoint seems sound. The analysis today suggested no statistically significant differences in safety profile between the candidate vaccine and the established vaccine. But we only have 2,000, 3,000 person years of follow-up.

So we can only make that statement about common events. And I think that is accurate. And I think the proposal to follow 30,000 individuals and allow us to make inference about more rare events that occur with an instance of one in 2,000 also sounds accurate.

DR. DAUM: Thank you very much. Dr. Bennink?

DR. BENNINK: I would like to ask the FDA in

terms of precedence or historical aspects of looking at these things, what do you consider is risk? Or what kind of numbers are you looking at in terms of what you see from benefit, what you see from these risk? Or are these numbers that typically would be what you in the past, it's acceptable?

DR. GRUBER: Let me try to answer in the following way. There is no absolute number that FDA says, by which we decide that the safety database is adequate or not adequate. It really depends on the type of events, adverse events use, adverse events, or adverse events of special interests. You heard it all this morning, being observed in the pre-licensure face of the clinical studies.

That being said, if you ask me if I want to compare it with safety databases that we have seen, to support an approval of products that are combined with novel adjuvant, the safety database, the pre-licensure safety database, or substantially larger than what is before us. But again, there are no absolute numbers. It all depends on the observations that are made in the pre-licensure phase.

DR. DAUM: And I would submit that we are here to advise them. So I think it is your call as to what advice you care to give. That is a twist to your question.

DR. MURPHY: I guess I am responding a little bit to the fact that this is a new adjuvant, and it really has enormous potential if it works well, and is safe, for perhaps other vaccines. We would like to be certain that this is safe for the US public because there are implications for the existing vaccines. If it turns out that we do have a safety signal down the line it raises questions in the American public whether the other vaccines are really a problem.

So I guess I would favor that we have a pretty secure feeling about this vaccine both because it provides a basis for future vaccines but also in the context of this vaccine, it protects our programmatic interests for the current vaccines.

DR. DAUM: Other comments on safety before we vote?

DR. TACKET: I appreciate the comments about the need for more, larger numbers. But I want to just interject the point that this vaccine, the kinetics of the immune response to this vaccine is very impressive in a comparison to what is currently available. So I think we need to balance the numbers of hepatitis B disease that we might be preventing while we are collecting, or that we may be missing while we are connecting more safety data.

So there is a benefit to be had immediately in terms of the rapidity of the immune response and the height of the immune response, that we will not have if we continue to accrue many, many more participants in the pre-licensure studies.

DR. DAUM: Thank you. Can I ask you a question in follow-up? In slide nine from the sponsor's presentation, we saw that hepatitis B was going down in all age groups. And there are one and two, depending on how you look at things, vaccines licensed on the market. And so is your concern still there in spite of the decline of those markers? Or should we get more safety data before going ahead with this?

DR. TACKET: I was specifically thinking of the kinetics of the protective response, which is so much sooner with this new vaccine than with the old. So that interval of prevented cases is something that we should consider.

DR. MURPHY: I would just like to reiterate that I think there is a strong sense that a vaccine like this would have huge advantages. And I think some of those advantages were listed, very nicely set out by Dr. Schaffner and Poland. So I don't think that we have eliminated enough hepatitis B in the US to make this an

irrelevant question. I think it is still relevant.

DR. DAUM: I think you misunderstood me. I didn’t mean to suggest that it was irrelevant. I think the question is, if there are safety concerns and issues that do clarification before licensure, is there a rush to license this in terms of preventing cases and having nothing out there to prevent them with?

So I don’t disagree with anything you said at all.

DR. GELLIN: We are talking about safety, but we always have to keep this in the context of benefits as well. In the beginning it was outlined why this product offers some advantages, and Melinda highlighted a few of those, that there are populations for whom the current products are inadequate. There are programmatic issues where reduced numbers of doses may be helpful as well.

So I think that we have to keep that context as well. As far as the performance of this vaccine, I learned today from the FDA that the height of the absolute antibody level doesn’t indicate duration of protection. That was news to me. I thought there was some correlation between that and duration.

So it seems that to me the focus is really on those populations who would benefit from this vaccine, that

wouldn’t benefit from other vaccines. So building off of what Melinda said, that this isn’t what was brought to the FDA, but the potential of maybe phasing this in, to focus this initially on those populations for whom the benefit is greater, that would allow an opportunity accrue a lot more information about its performance and it safety profile. And then based on that, then it could be seen in the context of a larger population.

Again, it is the question of where you draw the line between pre and post, and whether there is some intermediate place where rather than the entire adult population it can be targeted initially to those for whom its benefit is most needed. And then subsequently, an assessment on its role, because of its potential for some of the programmatic failures of a two-dose rather than a three-dose regimen.

DR. DAUM: Thank you, Dr. Gellin. Are there other comments or are we ready to look at question two in a voting way.

DR. BENNINK: Does that mean what you are suggesting is a more narrowed thing than just simply adults 18 through 70 years old? You are sort of suggesting an approval that is balanced?

DR. GELLIN: This is not what was typed on any of

the questions. But to me it is a way to introduce a vaccine into a broader population than is in the few that have been studied, and to gain more experience. But at the same time, to provide a product that has real benefits for whom existing products don't.

DR. DAUM: Other comments before we vote? Okay, I think we are ready to vote on question two.

DR. MARTIN: Dr. Daum, can I just make one comment before we vote? Can I make a comment?

DR. DAUM: Sure.

DR. MARTIN: I just want to make one more comment about size of the database and some unique aspects about the post-marketing surveillance in this disease target that are different than other targets, that I think may have an impact on the committee's deliberation. First of all there is a manuscript published by Ellenberg, et al. that looked at the size of the safety database and proposed that 2,500 subjects for the active database would be a typical expectation pre-licensure for the United States.

There were several criteria that were cited as might require expanding that database. And again, it was based on the ability to detect events that occur at a rate of one in 1,000. So if in fact it was the first vaccine to address a particular disease, you would need an expanded

pre-licensure database.

If it was a pediatric vaccine, you were going to be immunizing a more vulnerable population. If it was a vaccine that was likely to be recommended for universal use throughout the country, that would be another reason to have a large pre-licensure database. Or if it is a vaccine or a class of vaccines for which a prior safety signal has already been identified, i.e., rotavirus, none of those issues apply to this particular vaccine. I wanted to make that one point.

And the last one is with regard to the rollout, in the United States these years we immunized between one and three million adults per year. This vaccine will not get exposed to 10 million people in the first month of use, as if it were, say, a flu vaccine, a seasonal influenza vaccine.

So we have a product that has a relative risk of near one on almost everything that we have looked at today. A good safety profile can be handled with a careful pharmacovigilance plan in a context where it is not going to be exposed to 150 million people in one quarter of the year. And so it is a very different context to think about what kind of safety can be conducted post-marketing.

And it hearkens back to the conversation that

this committee had in September, which is, one can never exclude risk but one has to make sure that you have the right systems in place to detect risk if unexpected risks occur. And I propose that that is in fact what we have in this situation. There is no known risk today.

We have shown similar risk to a very safe vaccine. We have the systems in place to detect risk, and we are not going to expose 150 million people in the months of October and November to this product. Thank you.

DR. DAUM: Thank you for that comment. I would suggest that with regard to the Ellenberg criteria that the first point, is this a new vaccine to address a particular problem? The answer is yes, because of your adjuvant. And I agree with everything else that you said in terms of not the first.

So we are ready to vote. And I guess we just ask each committee member to push the button, whether they think the safety data are adequate for adults 18 through 70 years of age.

If it comes out to a no, you can start looking at the discussion point, that we could probably wrap up fairly quickly with respect to the conversations that we have had. Let’s get the vote done first.

MR. JEHN: We have five yeses, one abstain, and

eight nos. And the breakdown by person is as follows: Dr. Gellin is a no, Dr. Hutchens was a yes, Dr. Air, yes, Dr. Tacket, yes, Dr. Gray, yes, Doctor Cheung, yes, Dr. Murphy, no, Dr. Bennick was an abstain, Dr. Piedra, no, Dr. Marcuse, no, Dr. Wharton, no, Dr. McGinnis, no, Dr. Brady, no, and Dr. Daum, no.

DR. DAUM: Thank you everybody for voting. I guess now we will put up the discussion points and deal with them, and then we will adjourn the meeting. We are interested in the bottom discussion point which is, if no, what additional studies pre- and post-licensure are needed to further evaluate the safety of HEPLISAV?

I will ask no voters to begin by naming things that they think should be done. I think we are asked to distinguish between pre- and post-licensure. Is that correct?

DR. GRUBER: Yes, that is correct.

DR. DAUM: I can’t remember everybody’s vote, but just stick up your hand and chime in. Dr. Marcuse?

DR. MARCUSE: I would like to see a larger database somewhere of the order of 8,000 to 10,000. And I would like to see a more diverse, ethnically diverse population that is more reflective of the US population.

DR. WHARTON: I agree with Dr. Marcuse. I think

that a larger safety database and a more diverse population would both be extraordinarily helpful. Also, just to follow up on Bruce's comment before the vote, I do think that I think the answer to the question is a little different if we are not talking about the general population.

One strategy may be a focused effort on a higher risk population where the benefits of the vaccine would likely be greater, and that I would be comfortable with doing more of the safety assessment post-licensure in that population than I am in the general population.

DR. DAUM: Okay, the comment is noted. Dr. Piedra? You voted no. We want you to name what studies need to be done.

DR. PIEDRA: Correct. So I am in agreement with what was stated. But I would also say especially for me from an issue of safety as well as the concomitant vaccine administration, I know that they have it listed here as post-licensure. But I am also of the same opinion that I think it will be very relevant for some of the vaccines to have that type of information going forward.

DR. DAUM: Other people who voted no, comments about what should be done now?

DR. BRADY: I agree with everything that has been

said as far as pre-licensure for a larger in number and more diverse study population and also with the administration of other vaccines, only because I think this has to be looked at. As you stated, it is in fact a new vaccine, and the fact that you have a non known adjuvant.

DR. DAUM: Comments from this side of the table as to what should be done, even if you voted yes?

DR. MURPHY: I guess I would add that the comparison group would not necessarily need to be another hepatitis vaccinated group, but rather than general population.

DR. DAUM: And I would like to see any ongoing analyses be completed by the agency, and any patients with ongoing disease that have appeared in the trials so far be followed a bit longer and perhaps even studied a bit more closely. I think that is a very important part of this.

DR. GELLIN: I have laid out my case before. But I also think we have to be realistic that if you double or triple the number in the trial you are still looking for rare things to happen, and they are unlikely to light up if you have a study population of eight, 10, 15 thousand, if you are looking for one in a million.

Which is why the line between pre and post and thought that if there was a way where you could look at

this benefit-risk in a different way to get this vaccine used, as we heard from many people, and the people from the public about the need for vaccines, particularly in the populations who need them most, that might accelerate the experience.

And building on Trudy's comment, I think as we start looking at these new adjuvants there is going to be a lot of scrutiny about that experience. So that doesn't mean that we need to go slowly, but we need to go methodically.

DR. DAUM: Thank you. I would like to ask the agency if they have had the discussion that they hope for. I have a little trepidation to ask that question. But have we at least explored the agencies you hoped we would explore.

DR. GRUBER: Yes, we believe that you have explored all the issues and we had the discussions that we wanted, and that is very helpful to us in all further discussions. Thank you.

DR. DAUM: I would like to also perhaps end by saying that I think we have had a very difficult discussion today. I think there is a lot of enthusiasm around the table from yes and no voters, that this is a very promising vaccine approach.

And having said that we are not happy with where the adjuvant safety database is, nevertheless this is a very promising adjuvant. And I would like to thank the company very much for doing such a nice job laying out their side of the story, their data.

I would like to thank the agency's presenters for doing a wonderful job presenting as well. And I would like to most of all thank the committee members for speaking their mind. I think we have had a very thorough discussion. Thank you very much and we will see everybody next time.

(Whereupon, at 2:05 p.m., the meeting was adjourned.)