UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE MEETING

Tuesday,
May 26, 1998

The meeting took place in Versailles Rooms I and II, Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland at 9:00 a.m., Patricia L. Ferrieri, M.D., Chair, presiding.

PRESENT:

PATRICIA L. FERRIERI, M.D., Chair
NANCY CHERRY, Executive Secretary
MARY LOU CLEMENTS-MANN, M.D., Member
REBECCA E. COLE, Member
ROBERT S. DAUM, M.D., Member
KATHRYN M. EDWARDS, M.D., Member
DIANNE M. FINKELSTEIN, Ph.D., Member
HARRY B. GREENBERG, M.D., Member
CAROLINE B. HALL, M.D., Member
ALICE S. HUANG, Ph.D., Member
STEVE KOHL, M.D., Member
GREGORY A. POLAND, M.D., Member
DIXIE E. SNIDER, Jr., M.D., M.P.H., Member
ROBERT BREIMAN, M.D., FDA Consultant
CLAIRE BROOME, M.D., FDA Consultant
PATRICIA COYLE, M.D., FDA Consultant
RAYMOND DATTWYLER, M.D., FDA Consultant
THEODORE EICKHOFF, M.D., FDA Consultant
THOMAS FLEMING, Ph.D., FDA Consultant
DAVID KARZON, M.D., FDA Consultant
BENJAMIN LUFT, M.D., FDA Consultant

KAREN ELKINS, Ph.D., FDA Speaker
DANIEL R. LUCEY, M.D., FDA Speaker

PRESENT: (Cont'd.)

YVES LOBET, Ph.D., Sponsor Rep
DENNIS PARENTI, M.D., Sponsor Rep
ROBERT PIETRUSKO, Pharm.D., Sponsor Rep
ROBERT SCHOEN, M.D., Sponsor Rep
VIJAY SIKAND, M.D., Sponsor Rep
ALLEN STEERE, M.D., Sponsor Rep

HOWARD R. SIX, Ph.D., Public Comment
KAREN VANDERHOOF-FORSCHNER, MBA, MS, CLU, CPCU

ALSO PRESENT:

DANI DeGRAVE
CAROLYN HARDEGREE, M.D.
DAVID KRAUSSE, M.D.
FRANK ROCKHOLD, Ph.D.
ELKE SENNEWALD, Dr. rer.pol

AGENDA

P-R-O-C-E-E-D-I-N-G-S

9:03 a.m.

CHAIRPERSON FERRIERI: Good morning, everyone. I would like to bring the meeting to order. I am Patricia Ferrieri from the University of Minnesota Medical School and the Chair of the Vaccines and Related Biological Products Advisory Committee. We have a very busy agenda for the whole day. To begin, I would like to turn the meeting over to Nancy Cherry from CBER for various administrative issues. Nancy?

MS. CHERRY: Good morning, and I would add my welcome to Dr. Ferrieri's. I have a conflict of interest statement or a meeting statement to read, and it includes some announcements. This announcement is made a part of the record at this meeting of the Vaccines and Related Biological Products Advisory Committee on May 26-27, 1998. First, we would like to acknowledge and welcome the new members of the committee, Drs. Robert Daum, Dianne Finkelstein, Steve Kohl and Dixie Snider. Another new member, Dr. Kwang Sik Kim, was not able to be here today but will join us at the table tomorrow. Two other members of our committee, Dr. Ada Adimora and Mary Estes are absent from this meeting.

Second, you may wonder why your agendas start with Session 2. It was because there had been a closed session planned for early this morning, that was Session I. When that was canceled, everything else had already been numbered Session 2, Session 3, and Session 4, so we did not go

back. So, I apologize if you are confused by your agenda.

Then, under the authority granted under the committee charter, the Director of FDA's Center for Biologics Evaluation and Research, or CBER, has appointed the following individuals as temporary voting members for all committee discussions: Drs. David Karzon, Theodore Eickhoff, Thomas Fleming, and Robert Breiman. Additionally, the Director of CBER has granted voted privileges to Drs. Claire Broome and Benjamin Luft for the session on Lyme disease. In addition, the lead Deputy Commissioner of FDA has appointed Drs. Patricia Coyle and Raymond Dattwyler, who are consultants in the Center for Drugs Evaluation and Research, as temporary voting members for the discussion on Lyme disease. Finally, Drs. Charles Carpenter, Randall Holmes, Alison O'Brien and Nathaniel Pierce have been granted voting privileges during the session on cholera vaccine. During the discussions on oral polio vaccine labeling, we will be joined at the table by Drs. Geoffrey Evans of HRSA and Ms. Sandy Rovner, who has been appointed as a patient representative for the session.

Based on the agenda made available and on relevant data reported by participating members and consultants, all financial interests in firms operated by CBER

that may be affected by the committee's discussions have been considered. In accordance with federal law, the following individuals have been granted waivers which permit them to participate fully in the committee discussions on the inclusion of a boxed warning on package inserts for vaccines: Drs. Clements-Mann, Edwards, Ferrieri, Greenberg, Hall, Poland, Finkelstein, Kim and Daum. In addition, Dr. Daum has disclosed a potential conflict of interest which has been deemed by FDA as not requiring a waiver, but does suggest an appearance of a conflict of interest. A written appearance determine under 5 C.F.R. 2635.502 of the Standards of Ethical Conduct has been granted to permit Dr. Daum to participate in the discussions of Lyme disease and on the discussion on inclusion of a boxed warning on package inserts for vaccines.

The Food and Drug Administration Modernization Act of 1997, Section 505, included a new description of conflict of interest. Accordingly, the following individuals have been granted waivers which permit them to participate fully in the committee discussions: Drs. Edwards and Daum for Lyme disease, cholera, and inclusion of boxed warning for vaccines, and Dr. Greenberg for the discussion on cholera and for the boxed warning on package inserts for vaccines.

Additionally, it should be noted for the record that Dr. Raymond Dattwyler is negotiating to present a general lecture on Lyme disease supported by SmithKline. We should also note that Dr. Patricia Coyle consulted on one occasion with SmithKline in 1995. At that time, she reviewed monkey data pertinent to the vaccine which is not expected to come before this committee. She did not review human vaccine data.

Regarding FDA's invited guest, Ms. Sandy Rovner, the Agency has determined that her services as a patient representative are essential to the discussions on the inclusion of a boxed warning on package inserts of vaccines including oral polio. Ms. Rovner has no financial interests to report.

In the event that the discussions involve specific products or firms not on the agenda for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the public record. Screenings were conducted to prevent any appearance, real or apparent, of conflicts of interests of statements, and appearance determinations addressed in this announcement are available by written request under the Freedom of Information

Act. With respect to all other meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they wish to comment on. Dr. Ferrieri?

CHAIRPERSON FERRIERI: Thank you very much. I would like to start then by introductions from the committee members. If we could start on my very far right with Dr. Poland. Give your institution, please.

DR. POLAND: Greg Poland, Mayo Clinic, Rochester.

DR. EDWARDS: Kathy Edwards, Vanderbilt University, Nashville.

DR. HUANG: Alice Huang, CalTech.

DR. SNIDER: Dixie Snider, Centers for Disease Control and Prevention.

DR. GREENBERG: Harry Greenberg, Stanford University and the Palo Alta VA Hospital.

DR. CLEMENTS-MANN: Mary Lou Clements-Mann, Johns Hopkins University.

DR. DAUM: Robert Daum from the University of Chicago.

MS. COLE: Rebecca Cole, Consumer

Representative, Chapel Hill, North Carolina.

CHAIRPERSON FERRIERI: Patricia Ferrieri, University of Minnesota, Minneapolis.

DR. KARZON: David Karzon, Vanderbilt.

DR. KOHL: Steve Kohl, University of California, San Francisco.

DR. FLEMING: Thomas Fleming, University of Washington, Seattle.

DR. EICKHOFF: Ted Eickhoff, University of Colorado.

DR. BREIMAN: Rob Breiman, National Vaccine Program Office.

DR. LUFT: Ben Luft, State University of New York at Stony Brook.

DR. BROOME: Claire Broome, CDC.

DR. COYLE: Pat Coyle, SUNY at Stony Brook.

CHAIRPERSON FERRIERI: Thank you very much. We may have another committee member join us who is not here yet. We will start the program, then, with the open public meeting. I would like to caution everyone what the rules of the committee are. You have to raise your hand to be recognized and then you will be called upon. Please give your name

before you speak because everything you say is recorded here today, whether you wish it or not.

MS. CHERRY: Your name and your affiliation.

CHAIRPERSON FERRIERI: Yes, thank you, Nancy. So we will start then with a request to speak by Dr. Howard Six from Pasteur Merrieux Connaught. Dr. Six, could you come forward, please?

DR. SIX: Good morning, members of the committee, members of the FDA, and ladies and gentlemen. Over the next few minutes, it will be my pleasure to update you of the progress of Pasteur Merrieux Connaught in the development of a candidate vaccine for the prevention of Lyme disease.

The vaccine carries a trade name called ImuLyme. It is composed entirely of the outer surface protein, which is the OspA or outer surface protein A. The protein in the vaccine is indistinguishable from that found in Borrelia burgdorferi, the agent that causes Lyme disease. The protein is cloned from or is produced by cloning from the B31 strain. Each half ml liquid dose is formulated to contain 30 micrograms of protein, and the protein is dissolved in a solution of phosphates and .03 percent saline.

Over the course of the last several years, we

have conducted five large clinical trials. We have had one Phase I and three that were considered to be Phase II. The first of those was in serum negative individuals and the second was in individuals who had a history of lyme disease, some of which were antibody positive at the time of vaccination and some of which were not. There was a large consistency lot trial and a Phase III trial, which I will describe in detail in just a couple of moments.

In each of these trials, we have followed the individuals for a full 24 months, as was the consensus of the 1994 Advisory Committee Meeting to assess the safety of Lyme vaccines. Also consistent with the recommendations from that meeting, we have restricted our assessment to individuals greater than 18 years of age.

The pivotal trial was a large, randomized, double-blind placebo control trial, multi-centered involving 14 sites in the northeast and the upper midwest. The recipients or volunteers either received two doses of 30 micrograms of OspA in the spring of 1994 or a placebo which consisted of phosphate buffered saline. At one year after the first immunizing dose, a booster dose was administered and blood draws were obtained before dose 3, after dose 2, after

dose 3, and an acute and convalescent sera was obtained from individuals suspected of having Lyme disease. The primary endpoint was the prevention of Lyme disease.

Inclusion criteria were individuals who were 18 years of age or older and in good health at the time of enrollment, and individuals who were considered to be at high risk of acquiring Lyme disease. That is, they lived in an area known to be endemic for Lyme disease, and they also had reasons for being outside either through their job or through hobbies so that they would be expected to be exposed.

The case definition was essentially that that was agreed to by the Advisory Committee Meeting in 1994 and finalized by agreement with the FDA. In essence, this meant that a person to be considered a definite case of Lyme disease had to have clinical symptoms at the time they were seen by a physician. Usually these were manifestations of early Lyme disease, primarily erythema migrans. Also, it required laboratory confirmation of the infection, either through a positive skin biopsy culture or through Western blot serology using the Dearborn criteria of sero conversion.

Shown at the bottom of the slide are a synopsis of the reactions that were seen from the more than 10,000

individuals that were followed over the two-year period. Briefly, the administration of the vaccine was not associated with an increased frequency in serious adverse events -- vaccine adverse events. There was an increase in frequency in the local and systemic reactions which were generally transient and mild and resolved completely within 72 hours. There was no increase in the frequency of serious adverse events associated with either the first two doses or the booster dose.

5,868 volunteers received the first two doses of the vaccine. 3,755 received three doses of the vaccine. As mentioned previously, the local reactions were mild to moderate and usually resolved within 72 hours after administration of the vaccine. Serious adverse events -- there were 6 percent incidence after ImuLyme and 7 percent after placebo. None of these were felt to be vaccine-related. Thank you very much.

CHAIRPERSON FERRIERI: Thank you, Dr. Six. We will move on with the program them.

MS. CHERRY: We have on other, Ms. Forschner.

CHAIRPERSON FERRIERI: Our next presenter is Ms. Karen Forschner from the Lyme Disease Foundation. Would

you come forward, please?

MS. FORSCHNER: Good morning, everyone. I am Karen Vanderhoof-Forschner. I chair the Board of Directors of the Lyme Disease Foundation. The Lyme Disease Foundation is the first and largest scientific non-profit dedicated to finding solutions to Lyme disease and other tick-borne disorders. Our Board of Directors includes a former Congressman, the scientist who discovered the causative agent against Lyme disease, business leaders, public health officials, and patients. 1998 marks our 10th year anniversary.

As you know, Lyme disease is a serious multi-systemic infection transmitted by the bite of several ticks. Lyme disease is a world-wide problem and was first discovered and described over 100 years ago in Europe. The first U.S.-acquired case was medically published in 1970 by Dr. Scrimenti in Wisconsin. 49 states have reported 112,000 Lyme disease cases to the CDC since 1980. Published articles prove that the actual numbers are 13 to 15 times higher or 1.5 million cases. This excludes those cases that fall outside reporting criteria.

Lyme disease is a country-wide problem not

limited to just hot-spots. As a matter of fact, by misportraying the disease as limited to a few northeast/upper midwest states and California, people in other parts of the country feel they are not at risk for Lyme disease until it is too late. Taking a look at one year's case reports, you can find that North Carolina, California, Texas, Tennessee, Ohio, Oklahoma, Oregon, Missouri, West Virginia, Alabama, Kansas, Nevada, Mississippi, Florida, Georgia, Illinois, Iowa and Kentucky counties in those states have more cases than some counties in hyper-endemic areas in New York and New Jersey.

Lyme disease causes both diagnostic problems, as the bull's-eye rash which is most distinctive we now know is not the most common, and testing is an iffy use for diagnosis. A study by the Society of Actuaries in the New York University Stern School of Business shows that Lyme disease can be very costly to society as well as individual families. A survey of 1,000 patients with difficult cases shows that it took on average 5 doctors to get diagnosed with Lyme disease at a cost of $60,000.00. To select out that group to those who just had the EM rash, it took on average 5 doctors and $60,000.00. So the hallmark rash didn't help those patients get diagnosed any more rapidly. 70 percent had

a known tick bite, 46 percent had a rash, 41 percent had a rash and a bite.

Lyme disease can be very costly. With the average case of $60,000.00 for this group, it comes to a total cost of somewhere between $1.5 to $2 billion per year. 23 percent of that is in lost income, 24 percent is in medical testing before the diagnosis, and then half is in the testing and treatment after diagnosis. 89 percent of that population were not symptom-free. Lyme is a multi-system disease with patients having an average of four organ systems involved. Equal involvement in this group was neurologic and rheumatologic problems being number one and two. Severe fatigue, ophthalmologic problems and cardiovascular problems follow up. The majority of patients had non-cash losses, those that are never measured for most of the published studies. 71 percent suffered mental anguish. 41 percent had physical damage, either neurologic or rheumatologic. 19 percent lost time at work and 17 percent lost time at school. 2.5 percent divorced and 1 percent died. Another study showed that 20 percent of new cases were severe enough to need IV medications.

At its worst, Lyme disease has shown amongst

some of these patients physicians that are either uncaring or so frustrated that the patients themselves are sometimes blamed for their ongoing problems. In reverse, sometimes patients are so frustrated that they accuse the doctors of underdiagnosing for personal profit.

In face of these many controversies and as a result of no perfect test, insurance companies are cutting off access to both diagnostic tests and treatments. 1998 and 1999 will be banner years for Lyme disease and other tick-borne disorders. El Niño and other factors will keep this disease in the headlines.

The alternative is now here, a safe and effective vaccine. One that holds the potential for substantially reducing case of Lyme, the cost to society, and the suffering not only amongst patients but the physicians too. I urge you to review the data and make a rapid and fair decision. I look forward to the day when additional makers of vaccines will jump in and start a very strong competition with a second and third generation vaccine and driving the price down.

I know that we all want to preserve good health. If you want to see the impact that Lyme disease has

on many families, I encourage you to watch the TV documentary that is airing on Saturday, May 30, this weekend, on the Lifetime Network channel at 10:30 Eastern and Pacific, 9:30 Central, and 8:30 Mountain Time. I thank you for your time and admire those that have both been in the vaccine trials and that have monitored and been involved in that. I consider you heros long-term. Thank you.

CHAIRPERSON FERRIERI: Thank you, Ms. Forschner. I extend the committee's sympathy to you and your family on the loss of your child from Lyme disease. We will move now to the open session on LYMErix, the recombinant lipoprotein OspA Lyme vaccine from SmithKline Beecham Pharmaceuticals with the introduction by Dr. Karen Elkins from the FDA. And following her presentation, we will move on then to the sponsors presentation.

DR. ELKINS: Good morning. On behalf of the Research and Review Division at CBER, I would like to add my welcome to today's session, which promises to be very interesting. We would like to ask the committee members to consider the safety, efficacy, and seasonal use of a new Lyme vaccine from SmithKline Beecham, and to provide advice on use in persons over 70 and on any additional studies that should

be considered. My particular purpose is to provide a brief overview to the subject at hand.

Borrelia burgdorferi is the causative agent of Lyme disease. There are three major species, all of which cause disease with somewhat different manifestations in Europe. However, in the United States disease is caused almost exclusively by Borrelia burgdorferi sensu stricto. This is a vector-borne disease transmitted by tick bites, typically the deer tick. In the natural history of infection, it is notable that previous infection does not necessarily provide protection against a subsequent exposure to Lyme disease.

As with all bacteria, there are a number of outer surface proteins, and one of the earliest to be characterized from this particular bacteria was designated outer surface protein A or OspA. This is a major component of the bacterial cell surface, and it has a number of biological functions. It has been reported to be a plasminogen receptor, and this property is thought to be important in the pathogenesis of the disease. OspA is also highly immunogenic and it is an immunomodulator being reported to cause B-cell proliferation and cytokine secretion in both animal and human

cells. This is a lipidated molecule and the lipidation is critical in immunogenicity and immunomodulatory activity of OspA, but not apparently in its function as a plasminogen receptor.

OspA appears to be a highly conserved molecule. Minimal sequence variation has been reported in OspA gene sequence to date from Borrelia burgdorferi sensu stricto isolates on the order of 1 to 4 amino acids being noted. Most interestingly, the expression of the molecule is locally regulated. OspA is expressed in high quantities on the surface of the bacterium when the bacterium is located in the mid gut of the tick, but is apparently down-regulated as the bacterium transverses to the salivary glands of the tick and the tick takes a blood meal, and further down-regulated as the bacterium enters the host.

In the literature, an association between anti-OspA immune responses and the development of Lyme arthritis has been noted. Specifically, this association appears operative in treatment-resistant chronic Lyme arthritis, a rare complication of late Lyme disease, in which patients treated apparently appropriately with antibiotics to the point of eradication of the bacterium nonetheless continue with a

course of arthritis. This has led to the suggestion that the arthritis has moved from an anti-bacterial response to an autoimmune response.

Treatment resistant chronic Lyme arthritis has been associated with anti-OspA antibodies as well as with certain Class II major histocompatibility genes, particularly certain DR4 and DR2 alleles. And this observation would be more consistent with a role for cell-mediated immunity in the pathogenesis of late Lyme arthritis.

FDA is aware of very recent data that further supports the hypothesis that cell-mediated immunity may be involved in the pathogenesis of treatment resistant late Lyme arthritis. In data that the sponsor will discuss in further detail today, it has been observed that synovial T cells from some people with treatment-resistant Lyme arthritis respond to full length OspA, particularly a particular peptide from OspA. This peptide binds to certain DR4 alleles, namely the same ones previously associated with late Lyme arthritis, providing a molecular explanation for the recognition of OspA. Further, the peptide shares sequence identity to some sequences in a human protein, leukocyte function antigen 1 or LFA-1, which is expressed on human T cells, particularly activated human T

cells such as might be present in an inflamed joint. Further, the synovial T cells from some patients with treatment-resistant late Lyme arthritis appear to respond to LFA-1 itself, leading to the hypothesis that LFA-1 is a candidate autoantigen, explaining the pathogenesis of this phase of the disease. On the other hand, it is not clear what, if any, implications these data, which relate to the natural history of disease, have for vaccination with OspA itself.

FDA has also recently become aware of preliminary data concerning T cell responses of vaccinees. In a small subset of patients, peripheral blood was collected to study proliferative and cytokine responses to OspA after the conclusion of the pivotal efficacy trial. In these patients, T cell responses to full length OspA and to the peptide in question have been detected. However, T cell responses to LFA-1 itself have not yet been studied. And it should be noted that in the pivotal efficacy trial, no apparent increase in the frequency of arthritis was noted in vaccinees as compared to placebo recipients. And this safety data will be discussed in further detail today as well.

OspA has also long been of interest for its

role as a protective antigen. Mice, dogs, guinea pigs and other animals vaccinated with OspA are protected against a subsequent challenge with virulent Borrelia burgdorferi, whether introduced by needle or by exposing vaccinated animals to Borrelia infected ticks. Further, human sera with anti-OspA antibodies are able to transfer protection to mice against a virulent Borrelia challenge, whether introduced again either by needles or by exposure to infected ticks.

So on the basis of pre-clinical studies as well as early clinical studies in Europe, SmithKline selected the particular formulation of OspA to be discussed today. The US IND for Phase II studies was initiated in 1994. The pivotal Phase III efficacy trial began in early 1995 and was completed in late 1996. After analysis of the data, the product license application and the companion establishment license amendment were submitted in 1997, and bridging studies for the final manufacturing scale-up were initiated in 1997, completed and added to the PLA in 1998, bringing us here today.

A note about the implication of vaccination with OspA for a diagnosis of subsequent Lyme disease itself. Many commercial ELISA kits use plates that are coated with whole Borrelia burgdorferi, and whole Borrelia grown in-vitro

do express OspA on their cell surface. Thus, vaccination with OspA may lead to false positive ELISA results when this method is used for detection of disease. However, the OspA band is not part of the standard criteria for interpretation of Western blots, and thus vaccination should not lead to false positive Western blot results when these criteria are applied. Further generation ELISA kits that will avoid this confusion are also under development.

So the formulation to be considered is 30 micrograms of recombinant lipidated OspA in .5 ml of phosphate buffered saline absorbed to aluminum hydroxide and containing 2-phenoxyethanol as a bacteria static agent.

The questions that we would like the Advisory Committee to consider as the day progresses are as follows. Number one, are the data sufficient to support the conclusion that the vaccine is safe for immunization of individuals 15 to 70 years of age? Number two, are the data sufficient to support the conclusion that the vaccine is effective against definite Lyme disease in individuals 15 to 70 years of age when given on a 0-1-12-month schedule? Number three, please comment on the use of Lyme disease vaccine in persons over 70 years of age. Number four, in the efficacy trial,

vaccinations were given just before the Borrelia burgdorferi transmission season at 0 and 1 month between January 15 and April 15 and then 12 months later between approximately February 15 and April 30. Should a similar seasonal vaccination schedule be recommended in the package insert? Number five, are there any additional studies that should be performed by the sponsor? And unless there are any very general questions from committee members, I think we should proceed to the sponsors presentation.

CHAIRPERSON FERRIERI: Thank you.

DR. PIETRUSKO: Good morning. On behalf of SmithKline Beecham Pharmaceuticals, I would like to thank the FDA and the Advisory Committee for allowing us the opportunity to review data on LYMErix, our new vaccine for the prevention of Lyme disease that is currently under review by CBER at this time.

The efforts of many researchers, investigators, and colleagues are appreciated as well as the family support in bringing this product forward at this time. SmithKline Beecham now also would like to publicly recognize the fine efforts of the CBER review team under the leadership of Dr. Karen Wilkins. Oftentimes, the truly remarkable efforts of the

Agency go unrecognized. This team worked diligently and provided valuable scientific input as well as prompt feedback during the review process.

Lyme disease is a medically important condition. LYMErix is a novel vaccine for the prevention of this emerging infection. It also has a unique postulated mechanism of action working in the mid gut of the tick. You will hear more about this later on in the discussions by Dr. Yves Lobet.

The presentation by SB will take approximately 90 minutes or less, and it is requested that questions be held by the committee until all presentations have been made since many questions may be answered during latter presentations. The agenda is outlined as follows. After a brief introduction and overview, Dr. Robert Schoen, clinical professor of medicine from Yale University School of Medicine, will describe Lyme disease with emphasis on the epidemiology of this emerging disease.

Following Dr. Schoen's presentation, Dr. Vijay Sikand who is primarily a family practitioner from East Lyme, Connecticut, will describe the need for the vaccine. Dr. Sikand sees many patients and a variety of medical conditions

including Lyme disease. He is also adjunct Assistant Professor of Medicine at Tufts University School of Medicine, and was one of the investigators who participated in the large controlled clinical trials.

Following Dr. Sikand, Dr. Yves Lobet, a senior scientist in R&D, SmithKline Beecham Biologicals in Rixensart, Belgium, will discuss the preclinical development of the vaccine, including how the vaccine possibly may work.

The next topic on the agenda is a discussion of the clinical experience with LYMErix from the large, double-blind, randomized clinical trial that was conducted in the U.S. in more than 11,000 subjects. This will be presented by Dr. Allen Steere, who is very well known to this committee and researchers in the field of Lyme Disease. Dr. Steere served as the coordinating investigator for this clinical trial and is the Zucker professor of rheumatology and immunology at Tufts University School of Medicine in Boston.

This will be followed by a presentation by Dr. Dennis Parenti, Director of Clinical R&D within SmithKline Beecham Biologicals. Dr. Parenti will discuss the immunogenicity and the safety data primarily from the pivotal study.

After Dr. Parenti's presentation, I will make a few brief concluding remarks and any questions from the committee will be fielded at that time.

As mentioned previously, LYMErix vaccine contains recombinant DNA-expressed lipoprotein outer surface protein A that is commonly abbreviated as OspA. It is expressed in E.coli and transformed with OspA gene from Borrelia burgdorferi sensu stricto species. Dr. Lobet will go into further detail during his presentation.

The production process is relatively standard for a recombinant DNA vaccine product. As can be seen by the flow diagram, the antigen is expressed in E.coli and undergoes a separation and purification process. LYMErix vaccine itself contains a single 30 microgram dose of lipoprotein OspA antigen per 0.5 ml. In addition, aluminum hydroxide is included in the dose of 0.5 mg as an adjuvant. A phosphate buffer is employed and 2-phenoxyethanol is included as a bacteria static agent.

SmithKline Beecham Biologicals in Rixensart, Belgium is responsible for quality control release testing of the product. This includes tests for identification, potency, purity and stability of the product. This is a listing of

all the tests that are done in the final container in Rixensart prior to release.

As mentioned previously, the IND for LYMErix was filed in the U.S. in February of 1994. Shortly thereafter, there was an FDA advisory committee meeting that was held in June of that year to discuss a clinical trial design for the efficacy and safety of a Lyme disease vaccine. All recommendations discussed at this meeting were subsequently incorporated into the clinical trial protocol that was initiated in January of 1995. Another advisory committee was held in April of 1996 to address criteria for evaluation of the vaccine in the pediatric population. The PLA was filed in 1997, and this was the first totally electronic submission for a preventive vaccine within the Office of Vaccines and Related Biological Products.

I just mentioned the June 1994 Advisory Meeting discussed various issues regarding clinical trial design. This included the case definition of Lyme disease, and at that time it was determined that the CDC case definition would not be sufficient for the clinical trial evaluation. The definitions of primary and secondary endpoints were discussed as well as a determination that safety and efficacy data

should be followed for a period of two years. Collection of data in subjects with a previous history of Lyme disease also was suggested. The committee's specific recommendations were incorporated into the study design. The efficacy criteria, case definitions, and results will be discussed by Dr. Steere in his presentation.

Another major focus of the April 1996 Advisory Committee Meeting was on the pediatric development of the vaccine. In addition, there were three theoretical issues that were discussed. This included exacerbation of Borrelia burgdorferi pathology in individuals that had a previous history of Lyme disease; alteration or attenuation of a disease presentation, a theoretical concern that the vaccine may concern the presentation of the presenting symptoms or actually mask the presentation with resultant asymptomatic infection, the disease going underground; and the third issue of concern was the induction of autoimmune arthritis due to production of anti-OspA antibodies.

Currently, the application is under review at the FDA. In addition, this year a filing was made in Canada. This has received priority review status and is currently under review.

Regarding the clinical experience with LYMErix, as of today more than 12,000 subjects have received at least one dose of the vaccine. This includes the approximately 5,000 subjects who received LYMErix in the controlled clinical trial as well as the placebo subjects who have been crossed over. In addition, 28,000+ doses have been administered. Over 300 children ages 15 to 18 years of age have been vaccinated in the controlled clinical trial and more than 1,200 subjects with a previous reported history of Lyme disease have also been included in those particular studies.

Based upon the results of the efficacy trial and these data, SmithKline Beecham is proposing the following indication. LYMErix is being proposed to be indicated for the prevention of Lyme disease and asymptomatic infection caused by strains of Borrelia burgdorferi endemic to North America. It will be indicated in adults and children 15 years of age and above, including individuals with a history of Lyme disease. The dosing regimen being recommended is a 30 microgram dose administered intramuscularly at 0, 1, and 12 months, and the same dose is being recommended for adults and children 15 years of age and above.

In summary, the manufacturing process by which

LYMErix is produced is both consistent and validated. It is produced in a facility whose experienced staff has produced vaccines for the U.S. market for many years. You will hear data presented this morning from Dr. Allen Steere that demonstrate LYMErix is efficacious. You will also hear data presented by Dr. Parenti, who will show that LYMErix also is highly immunogenic, safe, and well-tolerated. Now I would like to introduce Dr. Robert Schoen, clinical professor of medicine at Yale University School of Medicine, who will discuss Lyme disease and its epidemiology. Dr. Schoen?

DR. SCHOEN: Thank you, Bob. It's a pleasure to have an opportunity to appear before this advisory committee. My name is Robert Schoen. I am a rheumatologist in New Haven, Connecticut. I participated in the pivotal Phase III Lyme disease study that you will be hearing more about as an investigator at a site at Yale University where we enrolled approximately 1,000 volunteers as subjects.

Lyme disease is now the most common vector-borne illness in the United States. Lyme disease is both a new disease and a newly recognized disease. And to get a sense of what has happened over the past 20 years, I thought I would begin with a picture taken from Joshua Town Road. I

hope that you can see this decaying barn in a field which at one time was pasture. There was intensive farming in this area which has largely been abandoned. The forest is taking over again both in rural and suburban areas throughout the northeast, and this is perhaps seen better here than elsewhere, but this is a phenomenon throughout the area. This is a preferred habitat for deer and therefore deer ticks. So one aspect of the rise of Lyme disease in the United States is not mysterious. It is this change in habitat which is leading to an emergence of deer throughout much of the northern United States.

As you have already heard, there has been a very significant increase of cases of Lyme disease as reported by the Center for Disease Control beginning in the early 1980's. What I would like to do to give you a sense of background is to try to look a little bit behind this data to get a sense of the factors that are responsible for this increase in Lyme disease cases, which seems to continue right to the present time.

It is important to understand the ecology of the tick vector. One of the questions before you relates to the seasonal nature of this illness, at least in terms of the

onset of early disease. And as I think most of you are aware, multiple studies have shown data like this in which most cases of Lyme disease occur in the late spring and early summer. I have been looking at pictures like this for years, but it really came home to me at our site in New Haven, where we had almost 1,000 volunteers, as to how many individuals we would see during the period beginning right about now and extending into the early summer. This is because it is at this time that the nymphal tick Ixodes scapularis is active and feeding. We and our pets are innocent bystanders in this life cycle.

Another feature of the epidemiology of Lyme disease worth commenting on is this apparent bimodal distribution of early cases. One can see that children are certainly affected by Lyme disease. There seems to be not only in this data from Connecticut but in national data as well a falling off, perhaps these people are hard at work or at school, and then later in life in the middle years, both recreational and vocational activities presumably take people back outdoors and back out to Lyme disease exposure.

So are there factors that we can examine briefly behind the CDC data to give you a sense about what has happened with respect to Lyme disease over the past 20 years?

We have already talked about these environmental trends and the fact that the emergence of Lyme disease parallels the reemergence of deer in many habitats throughout the United States. There has also been a geographic expansion of disease. Clearly there has been an increasing public awareness, an awareness by physicians as well as a degree of over-diagnosis. And finally, as has been mentioned earlier, while this factor has received attention, less attention has been received to perhaps the more important problem of physician under-reporting, and I will touch on that.

Lyme disease has been reported in 48 states, but about 80 to 90 percent of the cases occur in this very populous northeastern corridor beginning about Cape Ann, Massachusetts down to this area. In addition, Lyme disease for some time has been recognized in the midwest in Minnesota, Wisconsin, and perhaps parts of Michigan. There are other case reports throughout northern California and adjacent states as well as, as has been mentioned, more scattered reports throughout the entire country.

Most of the increase in cases seems to occur not so much in highly endemic areas but in adjacent geographic regions. For example, in Connecticut in a 12-town region

around Lyme, which is highly endemic for the disease, the number of cases over the past five years or so has been fairly stable. But throughout the rest of the state, we see many more cases in other counties such as Fairfield County, Connecticut, Litchfield County, and New Haven County. And it is this geographic spread of the disease which seems to result in these additional cases.

Now as with any newly recognized disease, there has been an increasing physician awareness of the illness and awareness by patients through conventional channels. But in addition, Lyme disease has generated intense attention within the media and within the public. And some of this attention has been quite anxiety-provoking. For example, in this article which is now almost 10 years old, Lyme disease is described as a mysterious illness. And I think that probably all of the members of the Advisory Committee have a sense of this aspect of Lyme disease which has occurred over the past 20 years. But clearly this has some role in the tremendous interest in this illness as well as in its reporting.

Several lines of evidence suggest that Lyme disease is very much under-reported. Data from Maryland as well as this study from Connecticut all point to the fact that

perhaps only about 10 percent of cases or so are actually reported by physicians unfortunately. In this study done by Matthew Carter and associates at the Connecticut Department of Health, you can see that through an active surveillance, they identified about 1,000 cases among 400 physicians who maintain an active Lyme disease surveillance. With almost 11,000 practicing physicians in Connecticut, the number of cases reported was only about 10 percent of the expected reporting.

So in summary, Lyme disease is a rapidly emerging infection. It is already the most common vector-borne illness in the United States, and yet the incidence continues to increase. The illness is spreading geographically, primarily from highly endemic areas to adjacent regions. A number of factors influence CDC data, but one to keep in mind is this phenomenon of under-reporting, which may therefore underestimate the true health burden in terms of morbidity and cost of Lyme disease. Thank you for your attention.

DR. PIETRUSKO: Next we will have Dr. Vijay Sikand with a presentation on the need for a vaccine.

DR. SIKAND: Thank you. I am not sure -- I have a number of slides which are pictures, and if they don't

come out clearly, may I ask the person who is controlling the lights to turn them down just a little bit if that is true. My name is Vijay Sikand. I am a family physician in the Lyme, Connecticut area, where I have been for approximately 15 years. During that time, I have included academic research in Lyme disease as part of my primary care practice.

CHAIRPERSON FERRIERI: Excuse me, Dr. Sikand. Can you please use the microphone? Our recorders are having problems.

DR. SIKAND: Thank you for pointing that out. As I was just saying, I included research in Lyme disease as part of a primary care practice for a number of years. In early 1995, 1,200 volunteers came to my office to enroll in the SmithKline Beecham vaccine trial which we are discussing today. Almost three and a half years later now, greater than 92 percent of those patients are still providing me with clinical follow-up.

Why do we need a vaccine for Lyme disease? It has been almost a quarter century since Lyme disease was first described as an emerging infection in this country. During these years a number of factors, epidemiologic factors and clinical factors, have resulted in considerable morbidity in

burgeoning numbers of patients. This burgeoning load of disease as well as the increasing number of patients thus set the stage for prevention of this disease with a vaccine. Today, I will present to you some of the factors in a brief synopsis illustrating the need for a vaccine for Lyme disease. The illustrations which I will present to you, some of them are from my private practice and some of them are from the vaccine study.

The first factor is an epidemiologic factor, and this has already been discussed by Dr. Schoen. And that is that there is indeed a progressive increase in incidence of Lyme disease. The second factor also epidemiologic is the relentless geographic spread of this disease. There are new endemic areas being created annually and the disease burden is indeed growing.

The ineffectiveness of preventive measures which we attempt to practice is another important factor. We have tried various chemical and other means. Why have preventive measures, which are indeed important, not been effective in preventing an increase in cases of Lyme disease? And before I answer that question, let me underline the fact that I indeed believe it is important that we continue to

practice preventive measures because of co-infection with other illnesses besides Lyme disease. One obvious reason is that it is very impractical to practice certain protective measures. This individual in the Lyme, Connecticut area desires to do some outdoor work and does not want to be bitten by a tick. But the point is it is very difficult to ask children or anybody else for that matter to tuck pants into socks, et cetera, in the middle of July and August when the ticks are questing. We can certainly check our pets, but checking one's dog is indeed a Sisyphean task when the dog goes in and out of the house all day long. Probably the best protective measure, I think, in preventing Lyme disease is checking for ticks. Unfortunately, kids will only allow you to do this up to a certain age. And of course one must be vigilant with oneself.

More specifically, I think one of the important reasons to consider when thinking about why protective measures are difficult to utilize and be effective in preventing this disease is simply the nature of the Ixodid tick bite itself. The bite of this tick when it is infected transmits not only saliva infected with Borrelia burgdorferi, but the saliva also contains certain anti-inflammatory

substances which have an anesthetic effect. The end result of that is that tick bites in general are not noticed. In one study, over 80 percent of the patients who presented with definite Lyme disease did not remember a tick bite. It is therefore very hard to correlate the incidence of definite Lyme disease cases with preceding tick bites, and this is well known.

Furthermore, as has been eluded to earlier, the recurrence of disease in individuals is also well known. Unfortunately, in the majority of patients, the vast majority of patients, natural infection with Borrelia burgdorferi does not confer protective immunity. Difficulties in clinical diagnosis of this disease are also well known, and it is not my place today to give you an overview or detailed presentation of the clinical aspects of Lyme disease. However, a couple of issues that do spring up and which I would like to address are as follows. In particular, the spectre of asymptomatic infection is something that troubles me a great deal and troubles a great number of my colleagues who need to treat Lyme disease. The obvious analogy with syphilis infection with Treponema pallidus is there to consider. It is well known that Borrelia burgdorferi indeed

after asymptomatic infection can lurk or secrete itself in certain areas of the body, perhaps the central nervous system or perhaps the joint spaces, only to reappear months or maybe years later in the form of late stages of illness which are harder to diagnosis and treat.

In terms of the variability of Lyme disease, it is indeed a very variable infection, if not a very complex infection. In its very simplest form, it is erythema migrans, well localized, which we can all recognize and which we can all easily treat and from which most patients can get better. However, erythema migrans is not a single beast. Certainly this is the one which we easily recognize and which I just referred to. Before I continue with further slides, let me point out that the erythema migrans lesions you are about to see are all biopsy lesions which were laboratory proven to be caused by Borrelia burgdorferi. Sometimes erythema migrans can present as a pustular lesion as is this one in the popliteal fossa inviting the scalpel of a surgeon. Sometimes the lesions are vesicular in nature, inviting a diagnosis perhaps of herpes simplex infection. Sometimes our round lesion is actually triangular. Sometimes it doesn't even look round or red at all and invites a diagnosis of an

intertriginous fungal infection in the groin of this patient who was biopsied and proven to have Lyme disease. Sometimes the lesion is more plaque-like, inviting diagnosis of nummular eczema, psoriasis, or other similar lesions. Sometimes it is in unusual locations. Sometimes it is large like this one. Sometimes it is small with satellite areas. Sometimes it is multiple, appearing almost like urticaria or erythema multiforme. Sometimes, as in this individual who was a placebo recipient in the Lyme 008 SmithKline Beecham trial, it presents with other manifestations of early dissemination. This individual came in mainly because he was concerned about his face and it felt kind of funny and it was weak on one side. When I asked him whether he had had any unusual rashes, he said oh do you mean this one, and he showed me his arm with that EM. This is simply to illustrate the infranuclar 7th nerve palsy with which he presented. This patient, by the way, had no history of a tick bite or any unusual antecedent illness which he could remember.

The next slide is the electrocardiographic tracing of a 37-year-old mom from Lyme, Connecticut, mother of three. Generally healthy and no medical problems. Early on the day that this electrocardiogram was taken, she went to her

local health club and did her usual work-out, which went fine. However, when she came home that day, she noticed that she had some palpitations, a little shortness of breath, malaise, and things just didn't seem quite right, but she wasn't sure what. When her husband came home, she told him that maybe she had worked out a little bit too hard at the club. A few minutes later, he was reading the newspaper in an armchair and he heard a thump on the floor above. He ran up the stairs to find his wife unconscious briefly on the floor and called 911. On arrival at the emergency department, the patient presented with this tracing, which in retrospect was a superventricular tachycardia representing an escape rhythm. There was fortunately a very vigilant emergency physician who didn't understand quite why a 37-year-old healthy woman had completely passed out, and she had what was a relatively benign rhythm at that point. But he was wise and admitted her to the coronary care unit for further monitoring. Late that night and the early hours of the following morning, the CCU nurse noted that the patient had gone through progressive degrees of AV block culminating in complete atrial ventricular dissociation. A cardiologist was summoned. He inserted a temporary transvenous pacemaker. The patient was started on

intravenous antibiotics for about a week in the hospital followed by a few more weeks as an outpatient. This patient also had no history of a tick bite.

Besides the difficulties in clinical diagnosis, we are all aware that quandaries in laboratory diagnosis are rife. We rely pretty much on serologic testing in the United States today to assist us in diagnosing Lyme disease. Unfortunately, serologic testing, as with other infectious diseases, provides only indirect evidence of infection. When we order a serologic test, it just tells us that the patient has been exposed to Borrelia burgdorferi and doesn't tell us whether the infection is active or whether it is a past infection. It is probably worth noting, since I have learned a lot, that we don't have the clinical luxury in private practice that we had in the SmithKline Beecham trial in which we had baseline sera on all the patients who enrolled so that when they presented with symptoms, we could draw acute and convalescent serologies so as to compare them with each other and with baseline to better understand what symptoms they are presenting with. But your average physician in the office just can't do this. A patient comes in with symptoms or signs of Lyme disease and you have to make a clinical diagnosis and

it is not always easy and serology doesn't help. The fact that in particular the ELISA creates a great deal of false positive results is also problematic. In particular and commonly in infectious mononucleosis and other spirochetal disorders, even healthy people, juvenile rheumatoid arthritis and other autoimmune disease all can produce false positive results. Indeed, even with Western blotting recent reports have shown that infection with the agent of human granulocytic Ehrlichiosis can cause false positive Western immuno- blots. The false negatives that we deal with are generally caused by use of serology testing in patients who have early Lyme disease and in whom the serologic response with immunoglobulin M has not occurred to the extent to which it can be measured.

What do we have in the way of direct testing to try to see if the organism itself is actually there or evidence of it? Well, culture and PCR are what are out there right now. However, these are unreliable and impractical. Culture and PCR are certainly not warranted for the diagnosis of erythema migrans. The polymerase chain reaction is indeed sensitive in joint fluid. However, the diagnosis of Lyme arthritis does not require PCR testing since serology is almost invariably positive at that stage. Clinical conditions

such as complex neurological conditions when a test like sensitive PCR would be useful, unfortunately cannot be diagnosed that way because PCR and indeed culture are not sensitive for cerebrospinal fluid, nor are they sensitive for urine, blood, and other body tissues when later in the disease one might care to employ these techniques.

Finally, there are indeed many dilemmas in therapy. In particular, untreated or inadequately treated Lyme disease may lead to the chronic morbidity with which we are very familiar. Most commonly arthritis and the not common but complex neurological syndromes are what often result and which confront the primary care physician in the office diagnostically and therapeutically. These particular outcomes result in much more intensive, long-term expensive therapy, often in the form of long-term intravenous antibiotics. These are the patients who often are refractory to treatment. Indeed, these are the patients in whom symptoms seem to persist despite what we have given in terms of adequate antibiotic therapy by any known measure.

In conclusion, we need a vaccine for Lyme disease because it is increasing in incidence and geographic spread. We need a vaccine for Lyme disease because there are

problems in clinical diagnosis, its laboratory evaluation, and its treatment. We need a vaccine for Lyme disease because preventive measures are unfortunately ineffective. Lyme disease is indeed vaccine preventable. Availability of this vaccine would lead to a significant reduction in chronic sequelae and substantive morbidity. Lyme vaccine is thus a critical new public health approach to the primary prevention of Lyme disease in the United States. Thank you very much.

DR. PIETRUSKO: Next we will have Dr. Yves Lobet, who will discuss the treatment rationale for the development of Lyme vaccine. Dr. Lobet?

DR. LOBET: What I would like to do now is to introduce you to the practical data we have obtained in the development of an OspA-based vaccine. What is the initial rationale that led us to the development of the Lyme vaccine based on OspA. And finally I will explain to you in a little bit more detail what we think is the possible mechanism of protection with this vaccine.

First, let's take a look at the main actor in this story. Borrelia burgdorferi is a bacteria that belongs to the family of the spirochetes, to which also belongs Treponema pallidus, that is as has already been mentioned the

agent of syphilis. It has been isolated in 1982 by Willy Burgdorfer, and since then at least three different species has been shown to be pathogenic for humans. In the United States, however, only one species, Borrelia burgdorferi sensu stricto, has been found to be responsible for the disease.

Not much is known so far on how this bacteria induces Lyme disease. Most probably this disease and those symptoms are due to an inflammatory process that will occur locally in different parts of the body and where probably Borrelia is located. Usually very small numbers of spirochetes are found and are detected during an infection, and also Borrelia is able to persist completely undetected for several months to several years.

Our interest to develop an OspA-based vaccine was triggered in 1990 by the seminal work of two groups. The first one was the group of Marc Simon at the Max-Planck Institute in Freiberg in Germany that showed that you could protect immunocompromised mice, the skid mice, with the passive transfer of monoclonal or polyclonal antibodies against OspA. Very shortly later, Dick Flavell and Erol Fikrig at the Yale University in New Haven have shown that you can also protect those mice, but in this case immuno-competent

mice, by actively immunizing them with an recombinant form of OspA.

But what is OspA? As has already been mentioned earlier today, OspA is the major protein of Borrelia burgdorferi sensu stricto when you grow it in-vitro, as you can see on this slide here. It is a lipoprotein, that is, it is modified during its natural production by the addition of lipids at the end terminal end. It is surface exposed on the bacteria, and maybe more importantly it is present on the surface of the bacteria when the bacteria is within the tick.

Although a lot of work has been done around this molecule, it is largely unknown so far.

A possible concern about the use of OspA in the vaccine is its potential variability. In this graph, you see this is a comparison of the sequence of many different OspA's that have been obtained from different strains of Borrelia burgdorferi sensu lato, that is from the different afzelii, garinii, and sensu stricto strains, with the sensu stricto strains being the strains that you find in the United States. You see that here this scale indicates the variability or the further differences between the strains. Those other strains that are found and the Borrelia burgdorferi sensu stricto

species are very closely related and vary by only one, two, three or four amino acids. The strain we have used to develop our vaccine is ZS7.

We have initially produced three forms of OspA in E.coli. The first form is what is called -- in its final state, it is a mature part of OspA fused to AE1 amino acid of an unrelated protein. And the P-OspA is similar to pure OspA. The fusion is made with free immunoassay. And finally the lipo-OspA is the one that is similar to the Borrelia burgdorferi expressed protein. These three proteins have been initially compared for their immunogenicity, and very rapidly it occurred that MDP OspA was largely non-immunogenic or poorly immunogenic, and that those two molecules would remain to be further tested in challenge experiments or protection experiments. The lipoprotein OspA in all of the experiments we performed at that point and later on were always shown to be more immunogenic than NS1-OspA.

So in protection studies that we utilized in mice in collaboration with Erol Fikrig and Sam Telford at Harvard University, we vaccinated mice with OspA, both NS1 and the lipoprotein, and we challenged them with ticks that had been collected in an endemic area of Lyme disease on the East

Coast. Then we followed those mice by several criteria. The sero conversion to B39 is a way to monitor -- a very easy way to monitor for an infection. B39 is a protein against which the antibodies are developed very early in the infection. If you infect mice with killed Borrelia, you never develop anti-B39 antibodies, indicating that those specific antibodies are representative of an active infection.

As we see here, the non-vaccinated mice are, at least a large proportion of them, sero converted to B39. The ones that did not sero convert were probably not infected -- carried ticks that were not infected, as all of the ticks that you collect in nature are not infected. In the animals that were vaccinated, none of them sero converted to B39. Further, if you evaluate the protection by trying to cultivate Borrelia out of skin biopsies made in the ear, you find that again in the non-vaccinated group some of the mice were carrying Borrelia burgdorferi in their skin, while in none of the mice of the vaccinated groups were we able to find any spirochetes.

More interestingly, when we looked in the tick that fed on those vaccinated and non-vaccinated mice, we found that in the non-vaccinated mice 30 percent of the ticks were still infected after they dropped -- after the blood meal on

those animals, and 30 percent representing more or less the infection rate found in nature. While if you look in those vaccinated mice, you see the dispersement rate of infection decreases to 12 percent and in fact to zero in the lipoprotein vaccinated mice. If you go further and try to evaluate the average number of spirochete that you find in those different still infected ticks, you find in this one that is the only tick it was that fed on a vaccinated animal, the number of spirochetes was dramatically reduced. Together those results indicate that anti-OspA antibodies are able to decrease the number of spirochetes within the tick.

We performed a similar experiment in monkeys where monkeys again received both NS1 OspA and the lipoprotein OspA. They were followed to 42 weeks. Again, the lipoprotein OspA was shown to be more immunogenic than the NS1 OspA. And upon challenge, again all the ticks but one -- so 100 ticks -- all of the ticks that fed on the vaccinated animals, all of those ticks were cured of that infection, indicating again that OspA was able to kill Borrelia within those ticks. And also one of the vaccinated animals sero converted to a non-vaccinal antigen. Just to make sure we are not dealing with a healing infection, we immunosuppressed those animals for

several weeks and we were unable to detect the appearance of spirochetes in any of the vaccinated and subsequently immunosuppressed animals.

Together, as I have already mentioned, those results show that anti-OspA antibodies are able to kill Borrelia within the tick. And I would like to explain to you in two slides now how we think this could occur. Let me first show you what happens in the natural transmission of Borrelia. First as a legend to this graphic here. Here is the tick. On the left side here, this white bar, is the mid gut. The left part is the mid gut and the right part is the salivary gland. And this blue thing here is the spirochete. When the tick comes from an infected host, Borrelia is present exclusively in the mid gut and it expresses OspA. When it begins to feed, Borrelia is still in the mid gut and expresses OspA and is not transmitted directly from the mid gut to the host. In the next step, when the tick begins to feed, it ingests some blood and at that point the Borrelia receives a signals that induces two different things. First, it migrates into the salivary glands. And secondly, it stops expressing OspA. Once in the salivary glands, here Borrelia is able to be transmitted to the host. Now what happens when the ticks feed on a

vaccinated mammal? The two first steps are obviously the same. And then at this point when the tick ingests the blood, it ingests at the same time some anti-OspA antibodies. And those anti-OspA antibodies are able to kill Borrelia within the tick mid gut. And at this point, there is no Borrelia to be transmitted to the host anymore.

So in summary, we have expressed three different forms of the recombinant OspA. Two of them are able to induce a significant amount of bactericidal antibodies. And the immunization produced by those recombinant forms are able to protect against tick challenges as well as syringe challenges. The lipoprotein version of OspA is the most immunogenic form. And finally, the immunization of OspA protects with a very novel and unique mechanism, that is, it blocks the transmission of Borrelia from the tick to the host. I thank you.

DR. PIETRUSKO: Now, Dr. Allen Steere -- do you want to take a break now or would you like to go on?

CHAIRPERSON FERRIERI: I would prefer that we had a moment for any quick questions. We have five minutes before our break and then we will have Dr. Steere come up after the break. So committee members, any questions for this

part of the sponsors presentation? As I mentioned earlier, some of you may not yet have arrived. If you raise your hands, I will call upon you in the turn in which I have recognized your question. Dr. Snider, and I see several other hands. I will get to all of you in a moment. Dixie?

DR. SNIDER: Thank you. Dixie Snider, CDC. I remembered. With regard to the proposed mode of action, could someone elaborate a bit on the time it takes for these events to occur?

DR. PIETRUSKO: On a preclinical basis within the tick?

DR. SNIDER: Yes.

DR. PIETRUSKO: Okay. Dr. Lobet will answer the question.

DR. LOBET: Yes. The time between the moment the tick attaches to the mammal and it transmits Borrelia to the host. During this time it begins to feed and Borrelia goes from the mid gut to the salivary glands and then it can be transmitted is at least equal to 24 or probably 36 hours. So the antibody has plenty of time to work in the mid gut. It takes some time for Borrelia to initiate and migrate from the mid gut to the salivary.

DR. SNIDER: And if I could just follow-up, what do you think the mechanism of killing bactericidal activity?

DR. LOBET: Both complement mediated and non-complemented mediated bactericidal activity has been found. Now you may also envision a different mechanism which is not bactericidal in which you may block somehow the function of OspA in the tick mid gut. Because you may very well speculate that as OspA is expressed almost exclusively in the mid gut of the tick -- that is the only place in the cycle that Borrelia is expressed. It may play a role or should play a role there, and maybe non-bactericidal antibodies could also block the transmission.

DR. SNIDER: Thank you.

CHAIRPERSON FERRIERI: As an extension of that, have you shown in-vitro lysis of the organism or some other mechanism of kill in-vitro?

DR. LOBET: Yes. There are bactericidal tests that show that you can kill the bacteria in-vitro definitely.

CHAIRPERSON FERRIERI: Dr. Daum next, please.

DR. DAUM: My name is Bob Daum from the University of Chicago, and probably a question that just

reflects my lack of understanding of the situation. But if OspA is primarily expressed in the mid gut of the tick, I presume it survives there and isn't normally killed there and probably doesn't see these kinds of antibodies very often. I was intrigued by the comment that it is a surface protein of the organism and has very little amino acid heterogeneity. that is not usual for surface proteins that interact with the immune system because usually antibody pressure makes them quite heterogeneous. So I presume the lack of heterogeneity reflects the fact that it hasn't seen in its natural situation antibody very much in the mid gut of the tick. So what we are proposing here or what you are proposing here in a way is to introduce a large segment of the population that will become antibody positive. And I guess I would ask you if you would be willing to comment on the theoretical concern that if there were such a large group of people or a large prevalence of antibodies in the population that this would begin to apply selective pressure against this protein and that it would become quite heterogeneous indeed.

DR. LOBET: Okay. Humans should be considered as a dead-entity -- an unusual host for the bacteria. The vast majority of those bacteria are found in mice and in deer and

that is one aspect. So the number of bacteria you would find in humans would present a very small percentage.

The second aspect is that it would be unlikely that those -- even if you ever induced -- and with data showing that is not the case so far -- even if you induced some escape mutants, it would be very difficult for them to go back into nature and be propagated there. And even if they did, there is no pressure to select for them in nature as mice have not been vaccinated with OspA.

CHAIRPERSON FERRIERI: Dr. Edwards, did you have your hand up? No. Okay. Dr. Kohl first. The members of the panel here do not have to keep announcing where they are from but just your name.

DR. KOHL: Steve Kohl. The monkey studies were mentioned. I believe it is also the case that in the placebo monkeys there was no disease, and I wondered if the placebo monkey blood was able to exert some sterilizing effect or anti-spirochetal effect?

DR. PIETRUSKO: Okay. Dr. Lobet.

DR. LOBET: In the monkey study, indeed we haven't seen any disease. We haven't seen any disease, but all the placebo sero converted to multiple antigens of

Borrelia. I mean, it was very clear that even after 42 weeks, new antigens or new antibodies were still appearing indicating an active infection. That is one. Now those sera had no sterilizing effect because the ticks that fed on those animals were all virtually infected after the blood meal.

CHAIRPERSON FERRIERI: Dr. Kohl and then Dr. Luft and then Dr. Breiman, and then we will have to close. Sorry, Dr. Breiman next.

DR. BREIMAN: Thank you. It is Rob Breiman. Someone had made the comment that natural infection does not induce protective immunity, and yet it was my understanding that late infection does or is assumed to produce protective immunity, and that perhaps early infection when treated early does not. What is actually going on? Is there some protective immunity that occurs at some point?

DR. PIETRUSKO: That will be answered by Dr. Sikand.

DR. SIKAND: I made that comment. It is a good point. Unfortunately, this has never been prospectively studied. But anecdotally it has been said by many clinicians and researchers who have dealt with Lyme arthritis that patients who have a history of Lyme arthritis haven't been

known to develop Lyme disease clinically again. Presumably this is because they have presented with a very widely expanded antibody response. That is why I prefaced my remark with the statement that almost all patients or generally speaking patients don't get immunity from infection. Perhaps patients with Lyme arthritis or other late manifestations have a degree of immunity, but they are in the minority, number one. And number two, indeed this unfortunately has not been studied prospectively.

DR. GREENBERG: Go to Dr. Luft next, please.

DR. LUFT: I just want to comment on the issue of the heterogeneity. I noticed that you had presented the phylogenetic mouse of the B31, 297, and N40 strain. Do you think that the same -- these are all strains, I believe, that were ascertained in the northeast, in particular in Connecticut and New York. Do you think that there is the same level of homogeneity in strains acquired throughout the United States or even within New York State? That is my first question.

DR. LOBET: Okay. There are only a very few data on sequences of OspA from Borrelia collected in California, for example. But you see maybe a slightly higher

heterogeneity, maybe one or two more as a difference. But again there are only very few data available. That is one thing. The second aspect, I can answer this. Erol Fikrig with Sam Titfall has also conducted some tick chain studies with ticks that have been collected in California, and they show a similar level of protection with DS7 as has been shown with those ticks collected on the East Coast.

DR. LUFT: But there is more heterogeneity at the amino acid level?

DR. LOBET: A little bit, yes.

DR. LUFT: The other issue that I just wanted to have some clarification on is, I believe, having read the primate model paper that was by Mario Philipp, he had in his -- in the paper he had mentioned that in some of the immunized animals that although they do not have serologic evidence of infection or clinical evidence of infection, that by PCR he was able to identify DNA specific for Borrelia within those animals. Is there --

DR. LOBET: Those PCR -- those are cases where you get a PCR positive result and none on the triplicates. In each case for each sample, you have most of the time one or sometimes two or three of the triplicates that were positive.

While if you go back in the control animals, they were all -- when they were positive, all three triplicates were positive. So I am not sure this really represents Borrelia DNA. There is still a question there, I agree.

DR. LUFT: So your interpretation is that it is perhaps a laboratory error and as far as any difference in the quantity of DNA with in the sample --

DR. LOBET: This would be my easiest explanation for this.

DR. LUFT: Thank you.

CHAIRPERSON FERRIERI: One last short question. Dr. Kohl, did you have your hand up again?

DR. KOHL: Yes. I was getting back to the question of prior protection induced by Lyme disease. Are we then to believe that there have been no studies showing that people with EM have either a decreased risk or the same risk of EM compared to people who have never had EM in endemic areas?

DR. SIKAND: Perhaps one way to start to answer that question is to say that -- well, there are two parts to my answer. First of all, in terms of EM, in the SmithKline

Beecham study itself, there was one patient who developed erythema migrans, which was biopsied and laboratory proven to be caused by Borrelia burgdorferi in year one of the study. And the same patient indeed presented with erythema migrans in year two of that study and was biopsied again and proven to have Borrelia burgdorferi infection.

The second part of my answer to your question, which is indeed an excellent one because it is important in our addressing this issue, is that a certain percentage of the patients in the SmithKline Beecham study were sero positive at baseline by Western blot criteria. Amongst those patients, there were indeed patients who developed biopsied, laboratory-proven Lyme disease during the course of the study. So even if you have an antibody response to Borrelia burgdorferi as measured by Western blot criteria, you indeed can develop Lyme disease. So in answer to your question of has it ever been studied, yes, it has within this study. But when I said that there have not been studies in the past, I mean we have not taken numbers of patients with Lyme arthritis and followed them over the years and seen how many of them developed Lyme disease.

DR. KOHL: Those patients who were sero

positive or Western blot sero positive, were they OspA sero positive?

DR. SIKAND: I am sorry, the question -- were they anti-OspA?

DR. KOHL: Correct.

CHAIRPERSON FERRIERI: Is that data available?

DR. SIKAND: I am not sure I understand the question. I am sorry.

DR. KOHL: The patients who were sero positive by Western blot and then developed Lyme disease, looking at the Western blots, did they have a band showing that they had antibody against OspA?

DR. SIKAND: Well, the band against OspA is the 31 kilodalton band. They did not have that. And indeed, that is not one of the criteria which were used in the interpretation of the Western blot. So the 31 kilodalton band was not present. Indeed, one would also not have been able to determine if that band was present because that information was not available to investigators in order to keep them blinded.

CHAIRPERSON FERRIERI: Thank you very much. We are going to break. Before we do, I want to acknowledge two

other members of our panel who joined us after our introductions, Dr. Dattwyler sitting at my very far left. He is from SUNY Stonybrook. And on my right is Dr. Carolyn Hall, University of Rochester Medical School. We will reconvene promptly at 10:45.

(Whereupon, at 10:36 a.m. off the record until 10:51 a.m.)

CHAIRPERSON FERRIERI: We are continuing with the sponsors presentation for the next hour essentially before an FDA presentation. I believe we will start then with Dr. Steere. Again, we are continuing the sponsors presentation with Dr. Allen Steere.

DR. PIETRUSKO: I would just like to make one brief comment. There were questions on the immunogenicity, and that will be covered in the presentation by Dr. Parenti at a later time. So we will be able to go over that in much more detail for you. Now I would like to introduce Dr. Steere.

DR. STEERE: Thank you and good morning. It is my pleasure to report the results of the efficacy portion of the SmithKline Beecham Phase III Lyme disease vaccine trial #008. In this study, my role was that of coordinating investigator. All of the laboratory tests related to Lyme

disease were performed in my laboratory at New England Medical Center. I also saw some patients clinically to help in the assessment of difficult problems. But subjects were not entered into the study at New England Medical Center.

The study was a multi-center, randomized, double-blind, placebo control trial of 10,936 subjects who were enrolled by investigators at 31 sites in highly endemic locations for Lyme disease in 10 New England, Mid-Atlantic, and Mid-western states. These sites represent all intensely endemic regions of Lyme disease in the United states. The study participants were randomized to receive either placebo or the vaccine candidate which was administered on a 0, 1, and 12-month schedule.

Inclusion criteria included that the study subject must be healthy and 15 through 70 years of age. In addition, they must be at risk of acquiring Lyme disease because they reside in an endemic area for the infection or have frequent outdoor activities in summer in such an area.

Subjects were excluded if they had active Lyme disease or recent Lyme disease treated with antibiotics within three months prior to study entry. In addition, they were excluded if they had other illnesses that might interfere with

the assessment of Lyme disease including those associated with joint swelling or musculoskeletal pain. They were also excluded if they took medications that might interfere with the evaluation of Lyme disease such as chronic antibiotic therapy. However, individuals with a past history of Lyme disease were not excluded.

The first two injections were given in the winter and spring of 1995, prior to the 1995 tick transmission season. In addition, during the transmission season, they received monthly postcard reminders about safety and Lyme disease symptoms. This was during year one of the vaccine study. The third injection was given in the winter or spring of 1996, and they received three postcard reminders about safety and Lyme disease symptoms during the 1996 tick transmission season.

Four blood samples were drawn on all subjects at 0 or baseline, month 2, month 12, and month 20. The study end-date was November 15, 1996. Thus, the duration of the study for individual subjects was 20 months.

The primary study endpoint was based on vaccine efficacy for the prevention of definite cases of Lyme disease in year one. For reactogenicity and immunogenicity

determinations, all 938 subjects at one site, the Yale University site, completed four-day diary cards after each dose of vaccine or placebo. In addition, these same subjects had blood samples drawn at five time points, including at month 13, so that OspA antibody titers could be determined prior to vaccination and after each injection.

Demographic characteristics included that the mean age of the study subjects was 46 in both the vaccine and placebo groups. 58 percent were men and 42 percent were women in both groups. At study entry, 11 percent of the subjects reported a history of Lyme disease. Subsequently, we determined that 2.3 percent had serologic evidence of previous Borrelia burgdorferi infection at study entry.

Compliance with the study protocol was excellent. 99 percent completed the second visit and 95 percent completed all visits.

In an effort to detect all cases of Lyme disease, study subjects were encouraged to contact the investigator if they developed any symptoms that might conceivably be due to Lyme disease. Amazingly, during the first year of this study, 10 percent of the study participants were evaluated for suspected Lyme disease. In 89 percent,

Lyme disease was ruled out and other diagnoses were made. The remaining 11 percent met Lyme disease case definitions.

Extensive laboratory testing, including culture, PCR, and Western blots was done in a central laboratory at New England Medical Center. Similarly, in the second year, 6 percent of the study participants were evaluated for suspected Lyme disease. In 82 percent, other diagnoses were made. During that year, 18 percent of that population met Lyme disease case definitions.

Patients who met the criteria for Lyme disease were classified in three general categories: definite, possible, or asymptomatic infection. In order to meet the case definition for category 1, definite Lyme disease, patients were required to have one or more of the following clinical manifestations: erythema migrans, meningitis or cranial neuritis, musculoskeletal involvement requiring objective pain and swelling of a joint, cardiovascular involvement with a high degree atrioventricular block, and at least one confirmatory laboratory test. In subjects with erythema migrans, a photograph of the lesion was required.

This is similar to the CDC case definitions for Lyme disease, but we expanded upon their definitions because

of the ability to do more extensive laboratory testing and a prospective study than is the case in clinical practice. For example, in practice it is recommended that physicians treat erythema migrans without doing laboratory testing. Therefore, for surveillance purposes, the CDC case definition accepts physician-diagnosed erythema migrans without laboratory confirmation as a case of Lyme disease. In contrast, we required that erythema migrans be accompanied by laboratory confirmation of culture, PCR, or serology to be counted as a definite case. I should also point out that the availability of baseline serum samples allowed greater assurance of seropositivity, since sero conversion was always required for serologic support of the diagnosis.

Laboratory confirmation consisted of a positive culture for Borrelia burgdorferi from a skin biopsy sample, a positive PCR result for Borrelia burgdorferi DNA from skin biopsy, CSF, or joint fluid, or Western blot sero conversion which was defined as a negative result followed by a positive IgM or IgG blot. Serologic testing was done exclusively by Western blot since the standard ELISA test would be expected to give false positive results in subjects vaccinated with OspA. The blots were read by experienced technicians

according to the CDC criteria. Reactivity with the 31 kd OspA band was not reported so that investigators remained blinded.

Category 2 consisted of subjects with possible Lyme disease. This included participants with physician-diagnosed erythema migrans without laboratory confirmation and patients with flu-like illness accompanied by IgM or IgG Western blot sero conversion. This category was called possible Lyme disease because of the potential for misdiagnosis.

Category 3 included subjects with asymptomatic Borrelia burgdorferi infection as determined by IgG sero conversion by Western blot between baseline and month 12 during the first year or between month 12 and month 20 in the second year without symptoms suggestive of Lyme disease. I would point out that doing serologic testing on all subjects also allowed a check on our surveillance system. If subjects did not come to our attention when they had symptoms of Lyme disease, we would still learn who had sero converted that year, and all subjects were asked if they had had symptoms compatible with Lyme disease during the past year.

Category 0 non-cases were subjects who were evaluated sufficiently and did not meet any case definitions.

Category 9 were subjects in whom the evaluation was incomplete and data were insufficient to make an assessment. For example, a subject would be classified in Category 9 if they came for an evaluation of acute symptoms, did not meet criteria for Lyme disease, and did not return for follow-up as required by the protocol.

A data safety monitoring board provided oversight of the study. The board was chaired by Dr. Neal Halsey of the Johns Hopkins School of Public Health. The Board included experts in Lyme disease, vaccinology, and statistics. It monitored reports of possible adverse effects and they confirmed prior to unblinding the categorization of all cases. In addition, at the conclusion of the study they recommended that the placebo group be crossed over to receive vaccine.

Both an according-to-protocol and intent- to-treat analysis were performed. To finish the study according to protocol, subjects had to receive all three injections, comply with the protocol criteria, and complete all follow-up examinations. The intention to treat population received at least the first dose of vaccine or placebo. The results of the two analyses were quite similar. The according-to-

protocol or ATP analysis will be presented here.

In year one, 60 subjects had definite Lyme disease manifested as erythema migrans in all but one case, though two participants with erythema migrans also had facial palsy. The final definite case had a trigeminal neuropathy. Altogether, there were 20 definite cases in the vaccine group and 40 in the placebo group. Thus, the point estimate of vaccine efficacy was 50 percent and the lower limit of the 95 percent confidence interval was 14 percent.

In year two, 74 subjects had definite Lyme disease, again manifested in most cases as erythema migrans, 13 in the vaccine group and 61 in the placebo group. Thus, following three injections, the point estimate of vaccine efficacy was 79 percent and the lower limit of the 95 percent confidence interval was 61 percent.

It is important to note that Borrelia burgdorferi was isolated from skin biopsy samples of erythema migrans lesions in the majority of definite cases. In both years, the spirochete was recovered from approximately 70 percent of participants in both the vaccine and placebo groups. Thus, this is the first treatment study of Lyme disease in which the diagnosis was confirmed by culture in the

majority of patients.

In an effort to identify factors that might explain breakthrough cases in vaccinated subjects, a post-hoc analysis was done in which vaccine efficacy was analyzed in definite cases according to age, sex, and geographic location using Cox regression analysis with time of onset as the outcome variable. In this analysis, no significant variation was found in vaccine efficacy in either year according to age, sex, geographic location or time of onset of disease.

In an effort to determine whether vaccination altered the course of erythema migrans, the duration of the lesion was compared in vaccine and placebo recipients. During both years, the median duration of erythema migrans was similar in both the vaccine and placebo groups, suggesting that the vaccine did not alter or attenuate this clinical expression of Lyme disease.

Regarding possible Lyme disease cases, 7 subjects in the vaccine group and 9 in the placebo group were or had physician-diagnosed erythema migrans without laboratory confirmation in year one. Similarly in year two, five subjects in the vaccine group and six in the placebo group had this manifestation. Thus, in this category vaccine efficacy

was low during both years of the study. Although erythema migrans often has a characteristic clinical appearance, it may be mistaken for other dermatologic entities. This is presumably the reason that vaccine efficacy was not demonstrated in subjects who were thought by the investigator to have erythema migrans but lacked laboratory confirmation.

In year one, 27 subjects had flu-like illness accompanied by sero conversion as did 27 subjects in year two. For this category, the point estimate of vaccine efficacy was 21 percent in year one and it was 41 percent in year two. Let me point out that there is a mistake on this slide. The P value here is .01 and not .5.

Infection with Babesia or Ehrlichia, which are carried by the same tick that transmits Borrelia burgdorferi, may cause flu-like symptoms, and Ehrlichia may cause false positive IgM or IgG Western blots for Lyme disease. It is likely that some patients with flu-like illness and sero conversion had these other tick-borne infections in addition to or instead of Lyme disease.

Because of the propensity of spirochetes to establish latent infection, we made a concerted effort to identify subjects who developed asymptomatic sero conversion,

some of whom might subsequently develop active late infection. In the first year, two subjects in the vaccine group and 12 in the placebo group had asymptomatic Borrelia burgdorferi infection as determined by IgG Western blot sero conversion between baseline and month 12. Thus, the point estimate of vaccine efficacy was 83 percent that year.

In year two, all 13 subjects with this outcome were in the placebo group and the point estimate of efficacy was 100 percent.

This was a unique study. First, all the intensely endemic areas for Lyme disease in the United States were included in the study. Second, the occurrence of Lyme disease in the study population was documented by culture in the majority of cases. In fact, obtaining skin biopsy samples for culture and PCR was critical. Not only does this provide the best proof of infection, but 30 percent of cases would have been missed if suspected Lyme disease had been assessed by serology alone. Finally, we believe that all cases of Borrelia burgdorferi infection were detected in the ATP population, including both symptomatic and asymptomatic cases. It should be noted that approximately 30 percent of the cases were tested as having asymptomatic Borrelia burgdorferi

infection. However, after the conclusion of the study, two patients with asymptomatic infection who declined antibiotic treatment at that time subsequently developed Lyme arthritis. This experience confirms that patients may present with late manifestations of Lyme disease and proves that they have sero conversion prior to the development of symptoms. Vaccination appears to be particularly helpful in the prevention of this type of disease.

There were theoretical concerns that vaccination might change or attenuate Lyme disease and make diagnosis more difficult. This study shows that vaccination does not interfere with the ability to confirm the diagnosis of Lyme disease by culture, PCR, or Western blot. Moreover, vaccination did not mask, attenuate, or alter the clinical presentation of Lyme disease. It did not induce asymptomatic infection and it did not affect the duration of erythema migrans.

In conclusion, this study shows that a high level of protection from Lyme disease and symptomatic Borrelia burgdorferi infection can be achieved with three injections of the candidate vaccine. Following two injections, vaccine efficacy among definite cases of symptomatic Lyme disease was

50 percent, and following year two, it was 79 percent. Among subjects with asymptomatic Borrelia burgdorferi infection, vaccine efficacy was 83 percent during the first year and 100 percent during the second year. Thus, we believe that this vaccine was highly successful in the prevention of Lyme disease. Thank you very much.

DR. PIETRUSKO: Next we will hear from Dr. Dennis Parenti.

CHAIRPERSON FERRIERI: Dr. Pietrusko, when you introduce your speakers, could you please use the microphone? Our next speaker is Dr. Dennis Parenti.

DR. PARENTI: Thank you. This morning I will be presenting the immunogenicity data followed by a very brief discussion of our consistency and bridging trial data, and then I will complete my discussion by presenting the safety data.

As has previously been mentioned, the immunogenicity subset is comprised of all subjects from one site who were willing to undergo blood sampling at months 0, 2, 12, 13, and 20. Throughout the course of the project, we have evaluated two antibodies, total IgG anti-OspA and LA-2 equivalents. Today I will be presenting the IgG data for the

according-to-protocol population for subjects with evaluable data.

This next slide presents the sero positivity rates and GMTs of IgG anti-OspA in subjects who were sero negative at baseline. Sero positivity was defined as having a titer greater than the cut-off of the assay of 20 ELISA units per ml. As you can see, at month two 98 percent of the subjects were sero positive with a GMT of 1,227. At month 12, as expected, the titers had declined. But at month 13, one month after the third dose, all the subjects were sero positive and they had attained a titer of 6,005. I am going to skip down to month 24 here, which is one year after the third dose. At that time, you can see that 98 percent of the subjects are still sero positive with a GMT of 1,324, which is virtually identical to that which was obtained at month two, one month after the second dose.

This next slide is a reverse cumulative curve of month two IgG titers from three different subsets. The 20 vaccine failures from year one are in blue. The yellow line represents the subjects whose GMTs I just described for you. This is the immunogenicity controls from the one center. The third line in orange represents subjects who were considered

non-cases. These were subjects who were evaluated for suspect Lyme disease but not found to be cases during the study.

As you can see, the non-cases in orange and the immunogenicity subset in yellow have virtually identical curves, suggesting that the immunogenicity subset is representative of the entire study population. The other point that I would like to bring out is that the vaccine failures here in blue are obviously different than these other two groups.

In summary, there was a high degree of protection in year two which was associated with higher titers which were attained after three doses. The year one vaccine failures, as I have pointed out, have significantly lower titers than the controls. And at month 24, the titers were essentially equal to those attained at month two.

Before leaving the immunogenicity portion of my talk, I would like to point out that we have ongoing and some recently completed studies which specifically address the issue of alternative schedules, which would allow for increased flexibility and help to address the issue of seasonality. I have brought data on these studies and reverse cumulative curves if the committee would like to see those

during the question and answer period.

I would now like to briefly discuss our process scale effort. A clinical lot utilizing a 20 liter fermentation scale and a 2 liter purification scale was used in the Lyme 008 or pivotal efficacy trial. In study line 14, pilot lots consisting of a 20 liter fermentation scale and a 20 liter purification process were found to be consistent and equivalency was shown between these lots and the clinical lots. So on line 14, we created a bridge between these two. In line 19 -- I am sorry, the process was subsequently increased to 75 liters for commercial use, and in study line 19, we showed that those lots were consistent and again equivalent to the pilot lot studies. So in essence we have made an indirect bridge from commercial back to the clinical efficacy material.

I would like to switch now from immunogenicity and to present the safety component. The Lyme safety data base consists of data from the solicited Reacto Card population with all unsolicited events in year one. During year two, we collected medical conditions requiring a subspecialist evaluation. And during the entire study, including a four-month extension, we collected data on all

serious adverse events or SAEs.

SAEs were defined as any event which was fatal, life-threatening, disabling, resulted in hospitalization -- and I should add that that included outpatient or one-day surgery -- any condition which was associated with a congenital abnormality, with cancer, or just in the opinion of the investigator was a significant hazard. I should also add that we had asked that pregnancies and subjects who developed arthritis or arthralgia lasting more than 30 days in duration be considered as SAEs for the purpose of tracking these events.

Again the solicited reactogenicity population consisted of 938 subjects at one site and they filled out diary cards on the day of and for three days following each vaccination. We specifically solicited for the symptoms of redness, soreness, and swelling and for general symptoms of arthralgia, fatigue, headache, rash, and fever.

The data that I am going to be presenting is the intention-to-treat data or population. It is almost identical to the according-to-protocol data which is in your briefing document. As you can see, there is a statistically higher incidence of local injection site reactions in the

vaccine group as expected. For the general symptoms of arthralgia, fatigue, and rash, there was a statistically higher rate in the vaccine group, but that was not true of the events of headache or fever. I should mention that the vast majority of these events were mild to moderate in severity, and the median duration of these events was two days.

If we next turn our attention to the frequent unsolicited events occurring within 30 days of vaccination from the entire study cohort. You will see here also that there was a higher incidence of local injection site reactions in the vaccine group and also a higher incidence of frequent events of myalgia, fever, and flu-like symptoms of fever, chills, and myalgia. You will also note that there was a higher incidence of rash in this population as well. I should note that the incidence of arthralgia, which was significantly higher in the solicited diary card group was not significant in this particular population.

Moving from early events to late events, that is, those that occurred more than 30 days after vaccination. You will see that there was no difference in the incidence or nature of these events. There was no statistical difference for frequent adverse events, frequent being defined as those

that occurred with an incidence of greater than 1 percent. And there was also no statistical difference for late events as analyzed by body system.

As recommended by the committee, we collected 24 months of safety data. For serious adverse events, there were almost equal numbers of subjects, 581 vaccinees and 586 placebo subjects who reported SAEs. Although the number of SAEs reported is large, I would just like to remind you that again this included events such as outpatient surgeries, pregnancies, and this arthritis/arthralgia category of data that we had additionally requested. I would also mention that the number of SAEs is independent of attribution. The nature and incidence of these events were similar between the two groups. There were, again, no differences by body system, and an equal number of subjects experienced serious adverse events that were deemed either related or possibly related.

There were also no episodes of immediate hypersensitivity in the vaccine group. We noted no unusual patterns of adverse events, and there were no deaths that were attributable to the vaccine.

We felt it was very important to investigate whether subjects with previous Lyme disease were at any

increased risk for adverse events and we addressed this in two ways. We identified a subset of subjects who had a self-reported history of Lyme disease and compared their adverse events to their counterparts in the same treatment group who did not have such a history. We also performed the same analysis by evaluating subjects who had a positive Western blot at baseline and again comparing their adverse events from the same treatment group to a population whose Western blot was negative at baseline. The results of this analysis indicate that vaccine and placebo recipients who had a self-reported history of Lyme disease reported more frequent AE's than subjects who did not. And just to paraphrase this, again, subjects with previous Lyme disease, whether they were in the vaccine group or the placebo group, reported a higher rate of adverse events. The interesting thing to note is that they included multiple body systems including GI and psychiatric and other body systems as well.

When we look at subjects with a more objective criteria of having a positive baseline Western blot, vaccinees who were positive at baseline experienced adverse events with a similar frequency as those who had a negative Western blot.

At this time, I would like to return to the

three theoretical concerns which had been mentioned earlier. These concerns have been around since the inception of the concept of vaccination with OspA and have been previously discussed both with the agency and at the advisory committee. I would like to review these concerns since our pivotal efficacy trial was specifically designed to address these issues. The three concerns are whether vaccination would exacerbate Borrelia burgdorferi induced pathology, whether vaccination altered or attenuated the disease manifestations, or whether vaccination would induce an autoimmune arthropathy.

Let me address these one by one. Let me start by addressing the issue of exacerbation of Borrelia burgdorferi induced pathology. In a Phase II study conducted at Yale, patients who had previously well-diagnosed Lyme disease were vaccinated and monitored for adverse events. The study demonstrated that there was no evidence that the vaccines activated their previous Lyme disease symptoms, and there was no evidence that they developed Lyme-like pathology. In Lyme 008 again, I just recently discussed with you that subjects who had a positive Western blot at baseline were not at any risk of either early or late adverse events.

The second issue is whether or not vaccination

may alter or attenuate disease. You have just recently heard from Dr. Steere that there was no difference in the presentation of Lyme disease or the duration of erythema migrans in the vaccine group and that there was no increase in the incidence of asymptomatic infection. In fact, it was fairly protective against that particular entity. And again there was no effect of vaccination on the onset of disease nor did it increase late Lyme disease manifestations.

The third issue is whether or not vaccination would induce an autoimmune arthropathy. Again, it has been well known that Lyme disease patients rarely develop a chronic treatment resistant arthropathy associated with HLA DR4 or DR2 and that these subjects are somewhat unique in that they generate measurable anti-OspA titers. So the question that has been around for a long time is does anti-OspA cross-react with endogenous synovial proteins leading to an inflammatory arthritis in a small percentage of genetically predisposed patients. At this time, I am not going to answer this question right away, but I will ask Dr. Steere to discuss some recent laboratory work in this area.

DR. STEERE: Thank you. I have had a long interest in the study of Lyme arthritis. Particularly

puzzling has been the observation that a small percentage of patients with Lyme arthritis have persistent joint inflammation most commonly affecting a knee after prolonged courses of antibiotic therapy. In rare instances, this joint inflammation may persist for more than one year after antibiotic treatment. We have called this chronic treatment resistant Lyme arthritis.

In our experience, such patients have negative tests for Borrelia burgdorferi DNA and joint fluid after antibiotic therapy, suggesting that joint inflammation may persist after the apparent eradication of the spirochete from the joint with antibiotic treatment. We have identified immunogenetic and immune markers in patients with treatment resistant Lyme arthritis. These include an increased frequency of alleles associated with severe rheumatoid arthritis, particularly HLA DR-beta 10401 alleles. In addition, in a recent study of 32 patients with Lyme arthritis, the only significant difference between treatment responsive or treatment resistant patients was in reactivity with dominant epitopes of outer surface protein A. In these patients, OspA reactive T cells in the joints produced primarily interferon gamma and a pro-inflammatory response was

dominant in the joint.

We have considered whether chronic treatment resistant Lyme arthritis results from persistent infection in a protected niche in the joint or from the development of autoimmune phenomena within the joint. Our recent studies give a potential biologic mechanism in support of the autoimmune hypothesis. We identified that the dominant epitope of OspA presented by the 0401 molecule is located within amino acids 165 to 173 of OspA. A homology search and binding algorithm identified only human lymphocyte function associated antigen as a candidate autoantigen. LFA-1 induced T helper reactivity in most patients tested with treatment resistant Lyme arthritis, but it did not induce activity in those with other forms of chronic inflammatory arthritis. Molecular mimicry between this dominant OspA epitope and LFA-1 would provide an explanation for persistent joint inflammation after the apparent eradication of the spirochete from the joint with antibiotic therapy. The question is whether this potential for an autoimmune response within the localized pro-inflammatory milieu of the joint would ever be duplicated in vaccinated subjects. As part of the 008 vaccine study, we did cellular immune testing in two subgroups of

subjects. One was 100 consecutive subjects from one site. They were not selected because of symptoms. In these subjects, the T cells were obtained two weeks after the third injection at the time of the maximal recall response. The other group was 12 subjects in the entire study population with unexplained arthritis or tendinitis following injections in whom cells were sent for study at the time of symptoms. However, in all subjects, the cells were frozen and testing was not done until after the code was broken to maintain blinding of the study.

After the end-date of the study, we learned that 47 of the 100 subjects had received vaccine and 53 had been given placebo. Enough viable cells were available to do testing in 41 of the 47 vaccine recipients and in 44 of the 53 placebo recipients. In these subjects, T cell responses were determined to whole unlipidated OspA -- in fact, I would underscore that the preparation we used for this was unlipidated OspA, because one is wanting to see the T cell antigenic response without a mitogen response -- and to synthetic OspA peptides by proliferation assay. In addition, the supernatant fluids from these cultures were analyzed for Interferon gamma and IL-4 production by ELISA. To date, this

work has been completed in 39 vaccine and 24 placebo recipients. In addition, HLA typing has been completed in 40 vaccinated subjects. Thus, work has not yet been completed in all placebo recipients.

As shown in this figure, the magnitude of the T cell responses were usually quite low, both by proliferation assay shown here and by Interferon gamma production shown here. Nevertheless, I think that these responses are real because greater mean responses are seen with the dominant epitopes of OspA, both by proliferation and cytokine assays. In particular, let me point out peptide 8, which is the one that contains the cross-reactive sequence with human lymphocyte function antigen. Interferon gamma production could be detected in only a few subjects, and only one subject, a vaccinee, produced high levels of Interferon gamma to peptide 8. The value in that subject was off the scale shown here. It was 2,317 nanograms per ml.

For presentation here, the subjects were grouped according to the presence of DR-4 or DR-11 alleles, which correlate with the greatest and least risk of chronic Lyme arthritis. Six subjects with 0401 or 0404 alleles or had these alleles, and they had a higher mean response to whole

OspA and to peptide 8 compared with the 34 subjects with the other alleles. Conversely, nine subjects had HLA DR-11 alleles, and they had significantly lower mean responses to OspA and to peptide 8 than did the subjects with other alleles.

The T cell responses to OspA were then correlated with clinical information about adverse reactions in the 100 consecutive subjects from one site. Of the 41 vaccine recipients, 17 were reported to have had an adverse experience, most commonly pain at the injection site, compared with 21 of the 53 placebo recipients. However, the magnitude of T cell response to OspA or to each of the OspA peptides was not significantly different according to the presence or absence of these clinical symptoms. However, one subject in the vaccine group had a somewhat different clinical picture in that she had pain in the left shoulder, elbow, and wrist for three months following the second injection and paresthesias in that arm for 12 months. When this information was correlated with the laboratory findings, it was learned that she had the 0401 allele and that she was the one whose T cells produced high levels of Interferon gamma to peptide 8, the one with the cross-reactive sequence. However, she did receive

the third injection and her joint symptoms did not recur and her paresthesias did not worsen.

When the code was broken, it was learned that 12 subjects in the vaccine group -- I am sorry, that the 12 subjects who had unexplained tendinitis or arthritis were evenly divided between the vaccine and placebo groups. Two subjects, one in each group, had arthritis or arthralgia and paresthesias after the first or second injection lasting throughout the subject. The subject in the vaccine group had the 0401 allele and T cell responses to peptide 8 with Interferon gamma production. These laboratory tests have not yet been completed in the placebo recipients.

In summary, Borrelia burgdorferi infection of the joint may lead to autoimmune arthritis in genetically susceptible individuals apparently because of molecular mimicry between the dominant T cell epitope of OspA and human lymphocyte function antigen 1 within the pro-inflammatory cytokine milieu of the joint. Would such conditions ever be duplicated in vaccinated subjects? In the 008 study, no pattern of vaccine-induced rheumatologic symptoms could be discerned by comparison of the vaccine in placebo groups. However, with laboratory markers including HLA typing and OspA

epitope mapping, two subjects were identified who had the 0401 allele and T cell reactivity with peptide 8 resulting in gamma Interferon production, and both had joint pain and paresthesias lasting for months. If OspA vaccination induces joint symptoms, the clinical picture based on these two subjects may be one of self-limited arthritis, arthralgia, or paresthesias. Moreover, if OspA vaccination induces joint symptoms, it must be a rare phenomenon, much rarer than the genetic susceptibility itself. Thank you.

DR. PARENTI: As I mentioned previously, we addressed these issues in our study design, and we addressed them prospectively along with our DSMB, and I would like to present some of that data.

In the first year after two doses, the DSMB reviewed those subjects who had developed arthritis or arthralgia within 30 days of injection and lasting more than 30 days. The DSMB, after unblinding this by AE code, found that there was an equal distribution of the groups. At that point in time, they recommended that no further action need be taken and that the study continue. So subjects were offered dose 3.

The DSMB again reviewed this at the end of the

study after it had been unblinded when they reviewed all the statistical adverse event comparisons, and again concluded that there was no difference in the late onset of arthritis or arthralgia.

DR. FLEMING: Will you be showing us that last line -- the data for that last line?

DR. PARENTI: The data from the last -- oh, yes. This was also addressed for a third time just prior to the placebo subjects receiving open label vaccine. So the study had been unblinded, but the DSMB members had not been unblinded to individual subjects, and the DSMB realized that it was very important to address this topic again before the placebo subjects got open label vaccine, otherwise we would lose our control. So the DSMB created a subset of subjects of interest and they rerandomized them and their data were reevaluated in a blinded fashion by three DSMB members. The result again was that there was no statistical evidence for an inflammatory arthropathy.

The DSMB addressed this concern for yet a fourth time after reviewing the data that Dr. Steere has just presented, and once again found that there was no evidence of an autoimmune arthritis.

In summary, we believe that the vaccine has a very acceptable safety profile, that after the four-day diary card observation period adverse events are similar to placebo, and that there is no clinical evidence to support any of the theoretical concerns. Thank you.

CHAIRPERSON FERRIERI: Thank you, Dr. Pietrusko and your colleagues. We have time before Dr. Lucey's presentation for FDA if you could stand available. We will start with Dr. Edwards.

DR. EDWARDS: I am slightly confused about the expression of OspA in patients that have natural disease and wondered maybe if Dr. Steere could comment on the antibody responses that are generally seen in patients that have natural disease, whether there are differences in immune responses in late disease in patients that have the susceptible HLA locus, and finally whether patients that were immunized or patients that have this late disease or this chronic arthritis, if you could comment a little bit about the levels of antibody to OspA and their CTL responses.

DR. PIETRUSKO: Dr. Steere?

DR. STEERE: If I don't answer all of that, please ask me again. If I can remember it all. Only a

minority of patients have an antibody response to OspA near the beginning of infection and usually low levels, an ephemeral response that disappears. So most patients do not have an antibody response to OspA early in the illness. Instead, it is later during the course of arthritis that about 70 percent of patients with arthritis develop a response to OspA. It usually occurs near the beginning of prolonged episodes of Lyme arthritis. So in other words, Lyme arthritis is usually intermittent. Particularly at the beginning there are short attacks, and some people never develop anything other than that even in the natural history of untreated infection. Whereas, some patients will then develop more prolonged episodes of arthritis, and that is usually when one sees an antibody response to outer surface protein A.

In the recent study that we did comparing T cell responses in patients with Lyme arthritis, the only significant difference between the treatment resistant and the treatment responsive group was in reactivity to certain dominant epitopes of outer surface protein A. And antibody responses to OspA are usually the highest that you see in patients with treatment resistant disease.

DR. EDWARDS: So do you think the organism is

turning that gene on in those patients that have arthritis?

DR. STEERE: Yes. I think most of us think that is the most likely explanation. We have never been able -- and no one else has either -- to culture the Lyme disease spirochete from a joint. It has been very difficult to show that it is there other than by PCR testing, and we don't know in the natural history of the disease what the spirochete is like. But certainly Erol Fikrig -- and you may want to comment on this -- has spearheaded work to show that the spirochete can express different proteins at different locations in the body. So I think most of us would accept the hypothesis that at some point during the joint infection, the spirochete may turn on production of outer surface protein A again.

DR. PARENTI: If I could just add to Dr. Steere's comments. Allen discussed the late antibody response. In our study, when we looked at our immunogenicity subset and we looked at their baseline anti-OspA level, there were only 6 out of 900 or so who had any kind of detectable anti-OspA level. And of that, that represents less than one half of 1 percent. And when you look at those titers, they are barely above the assay level. So essentially within this

cohort of people in an endemic area, we could not find significant anti-OspA levels at baseline.

DR. EDWARDS: Were their antibody responses remarkably higher than those that had no antibody response?

DR. PARENTI: Their response was the same. They didn't show a booster effect, for example.

CHAIRPERSON FERRIERI: Dr. Tom Fleming next, please.

DR. FLEMING: Fleming. I would like to join the sponsor in thanking the investigators for a very informative trial with 20 months of follow-up. I am trying right now to get a better sense of the clinical interpretation of what we found. And I am going back to your careful developments and your introductory material as you describe the clinical course of infection. You characterized three major components or stages or steps. One is the early localized infection including the EM and constitutional complaints, and then early disseminated infection, and then late Lyme disease including chronic arthritis and neurologic abnormalities. It is quite clear from the data that the vaccinated individuals seem to be benefitted in three specific categories. Most notably in reduction in EM. There is also

some reduction in flu-like consequences or flu-like syndrome, and although I am not sure what the clinical relevance of this is, in asymptomatic disease.

But the essence then is the EM reduction. And looking through the data, it wasn't apparent that the placebo individuals through this 20-month period had documented cases of early disseminated infection or late Lyme disease. What is the timing of late Lyme disease? These latter consequences I might have thought would be the ones of most clinical relevance to patients. So in essence it looks as though there is a clear signal for reduction in this early localized infection EM manifestation. What can we glean from the data though beyond that?

DR. PIETRUSKO: Dr. Steere, would you like to talk about the late manifestations? I know you eluded to it earlier on in your presentation. Could you further elaborate?

DR. STEERE: The goal in terms of evaluating patients was to try to identify anyone who might conceivably have symptoms that could be Lyme disease. And I think showing that that was the case, that patients were trying to do that, that 20 percent of the study population -- and there were more than 12,000 people in the initial year -- were evaluated for

suspected Lyme disease. And when people did have Lyme disease, they were usually very early in the course. This was a group of people who were prime to recognize Lyme disease or were interested in trying to do that. And it wasn't the sort of population where somebody might let symptoms go for months and months before seeking evaluation for that problem.

What it suggests in this study population is that the great majority of patients do have erythema migrans as the initial manifestation of the illness and they were recognized and they were treated and nothing else happened in those people. There were a few exceptions. I mean, a person who presented with a trigeminal neuropathy. In the second year, there was a person who developed Lyme arthritis and met study protocol for being counted as a case though it was because of PCR positivity from joint fluid and that person was sero positive at baseline. So I think that he had the disease before study entry, but it became apparent during the study.

Lyme arthritis will usually develop within months. What is months? 3 months, 6 months, 12 months, even 16 months if it is going to develop. So we would have expected within a 20-month study that anyone who was going to develop Lyme arthritis would have. The same thing is really

true of neurologic involvement, but there is a greater range. It may start later in terms of the development of late manifestations of the disease, but still it would be the rare exception. So how I would look at it is that the majority of patients were recognized at the first clinical symptom of the disease, were treated with antibiotic therapy, and did not develop later manifestations of the disease. And what is more, we were testing serologically at the end of 12 months -- that is 12 months after study entry, but it is more like 6, 5, or 4 months after the tick transmission season -- and we found out who was sero positive and had no symptoms yet. We would presume that some of them would have developed symptoms if they had not been recognized at that time. In fact, patients were counseled about you have undergone sero conversion to the spirochete. It is not really know how this should be treated, but most people are given a course of doxycycline and we are happy to give you that. Most people accepted it and took antibiotic therapy and nothing else ever happened. We do know of two subjects who declined treatment at that time who subsequently in the next year developed Lyme arthritis.

DR. FLEMING: So in essence then in looking at the data, there is approximately a 1 percent occurrence of

Lyme disease diagnosis in the placebo, and the intervention has been effective in reducing the frequency of this by 50 to 80 percent, but it is essentially EM, and there is no direct information, at least in this trial, that the vaccine was additionally beneficial beyond the way these placebo patients were managed in reducing disseminated infection or late Lyme disease?

DR. STEERE: We do know that other people in the study did not develop manifestations of late Lyme disease. So we believe by early recognition of erythema migrans and antibiotic treatment that we prevented later manifestations of Lyme disease in that group and that the development of it in the other group, a number of them would have had asymptomatic sero conversion before they develop it and we recognized that. So they were treated with antibiotic therapy as well.

DR. FLEMING: Chair, just one last thing.

CHAIRPERSON FERRIERI: Yes, please.

DR. FLEMING: So to follow -- to make sure I am understanding, I think we are saying the same thing. Basically by careful surveillance and appropriate antibiotic therapy, even without the vaccine we are able, at least over a 20-month period, to prevent the occurrence of disseminated

disease and late conditions.

DR. STEERE: If one is surveying a population this carefully, yes.

CHAIRPERSON FERRIERI: If I were a lawyer, I would say you are leading the witness.

DR. PIETRUSKO: I think an important point here is also that the asymptomatic sero conversion was identified as a part of this particular study. Oftentimes that would not be recognized in normal practice because there are no symptoms and therefore the subject would not come in.

CHAIRPERSON FERRIERI: Dr. Greenberg?

DR. GREENBERG: You showed, I think, a correlation of antibody levels after two months and subsequent illness in the vaccine failures in the coming year. Do you have the same data for the second year?

DR. PIETRUSKO: Dr. Parenti will answer that.

DR. PARENTI: No. Unfortunately initially the protocol was designed to look at the month two data and vaccine efficacy in year one. Unfortunately in year two the only data that we have after the third dose comes from the immunogenicity subsets. So it is a very, very small number of subjects.

DR. GREENBERG: One other question. Do you have any long-term follow-up subsequent to the end of year two that is on the maintenance of antibody level? You showed that at the end of year two it was just about the same as after the second month. Do you have anything like the end of year 3? Were patients followed?

DR. PARENTI: Yes. We obviously have a booster strategy program, and we have continued to follow those initial vaccinees for a couple of years now. We also have two other cohorts. One group has received an additional dose at month 24 and we are following them long-term. We have a group that are now receiving yet a fifth dose and we plan to be following them for the next couple years. We will be following -- we will be trying to determine the drop-off of antibody kinetics or the drop-off of the curve, and obviously when put together with a correlate, we hope to come up with a cogent booster strategy.

CHAIRPERSON FERRIERI: Dr. Claire Broome is next.

DR. BROOME: Two questions. One for Dr. Parenti. When you look at your two-month titers in the cases, have you broken that out by the interval between the vaccine

reception and the onset of the case, i.e., do you see a further correlation between the post two-month titer and the timing of the case?

DR. PARENTI: We have looked at the onset of disease in these subjects, and there is no tool. The onset of the disease is the same. We have not specifically looked at --

CHAIRPERSON FERRIERI: Use the microphone, please.

DR. PARENTI: We have also looked at their onset titer at the time of disease as well. So we have looked at both what they had at month two and when they came in for their acute evaluation, we looked at their titers there. And we have also looked at when they came back a couple of weeks later for their convalescent titers -- when they came back for their convalescent bloods as well.

DR. BROOME: But I would just be curious -- looking at the two-month with the interval between vaccine and disease. Because I think once they come in with disease, it is very difficult to interpret the titer level. My second question was to Dr. Steere, and it relates to your category of flu-like illness. I would like to know what were the

intervals at which you obtained the sera to document sero conversion. As we all know, flu-like illness is a pretty nondescript category. And I would like to be reassured that what you are looking at is sero conversion very tightly defined around the times of the flu-like illness as opposed to your category of asymptomatic sero conversion, which obviously relies on the difference between the two-month and the 12-month serology, as to whether those categories are really different.

DR. PARENTI: If I could go back to one of the comments that you made, you said that it would be difficult to assess antibody levels once people are infected. But in fact the natural response to infection is not to have any anti-OspA. So when we looked at the placebo subjects who were culture positive, they developed no anti-OspA at all. When we looked at the vaccinees who were infected, they developed no boost at all. When we looked at the vaccinees who were vaccine failures later in the year, they again had no boost. So I think that the response, even at an acute specimen or even a convalescent specimen, would be valid since we rarely essentially have not seen any boost in anti-OspA as a result of natural infection.

CHAIRPERSON FERRIERI: We have several other members of the committee, and you will have your turn. We will start with Dr. Karzon.

DR. BROOME: Could I get an answer to my question on the flu-like illness?

CHAIRPERSON FERRIERI: I am sorry, Claire.

DR. STEERE: We had a baseline sample on everyone, and we also had a month-two sample on everyone. So that would have been obtained in the winter and spring of 1995. In year one, the flu-like illness was assessed usually within one to two to three to four months after that second sample. And so we were -- the definition required that by Western blotting the month two sample be negative, and that either the acute or the convalescent sera be positive. There were certainly a number of examples where the acute sample was negative, and it was the convalescent sample that was positive. And either the IgM or the IgG criteria would apply in calling that a case. But I would emphasize that the reason this category was called possible Lyme disease was because of the potential for misdiagnosis based on those clinical symptoms and that laboratory diagnosis. And as I explained, we know that Ehrlichia infection can cause flu-like illness

and also give you a false positive Western blot for Lyme disease. As a matter of fact, we have done now serologic testing for Ehrlichia and Babesia as well as PCR testing, and when we excluded people in a sub-analysis who had evidence of co-infection, we found that in the people who had only evidence of Borrelia burgdorferi infection that vaccine efficacy in year two was just as high in the flu-like symptom cases as it was in the definite cases. That is what really makes me think that the problem with that category is the co-infection, and that it was certainly the right thing to call that possible Lyme disease rather than definite Lyme disease.

CHAIRPERSON FERRIERI: As we proceed, the questions need to be brief and the answers brief. Dr. Karzon?

DR. KARZON: The availability of Western blot in the titer fashion makes me consider the titer itself and its role in preventing infection or altering infection. There are many infectious diseases that we know about where antibody would be singled out as useless unless we knew that a given titer or titer range more accurately is necessary to prevent infection. Respiratory syncytial virus is a good example of that.

The very nice curve that was draw of Western

blot titers would prompt me to ask if you did a scattergram of individual "breakthrough" and protection? Do you get a threshold titer that would be a guide to what sort of expectancy we should have for antibodies? But a part of that question is exactly what is the epitopic sequence that is seen by that antibody? How much substitution can you have? Are there variable amino acids within that epitope? How does it compare to cross-reacting epitopes like LFA? There are questions that are put in the package because they pertain to the specificity of the titer. DR. PIETRUSKO: Okay, Dr. Karzon. I will have Dr. Lobet talk about the specificity response and then some of the other questions we will have Dr. Parenti respond to you also.

DR. LOBET: For the ELISA titers that have been shown here, those were with polychromal antibodies, so recognizing only the epitopes on OspA. We don't expect to have any difference even with small variations. For instance, in the recognition of OspA even with the small differences in the sequence. That is one part.

Even if you use LA-2 equivalents, LA-2 being a monochromal antibody that is known to be both bactericidal and protective in a mouse mother when you transfer it passively.

And we have an assay that allows us to monitor the amount of LA-2 equivalent you find in antiserum. I would not expect any difference in the recognition of the OspA you find in the United States for the following reason. All the isolates we have made from the clinical cases we have found here were similar to other known U.S. strains of Borrelia burgdorferi sensu stricto. And we know from previous experience that LA-2 will recognize all those different isolates. So we do not expect any modification of the response according to small variations in the OspA sequence.

DR. KARZON: Well, have you constructed epitopes and looked into this specifically? And I am probing this because there might be clues as to how you can make an antibody exactly what you want it to recognize, which might be safer in terms of seeing other systems.

DR. LOBET: The LA-2 epitope is not known for now. The only thing we know is that it is located on the second half of the molecule, which is rather vague. But there is no more information. We know there is a confirmation on the epitope also.

DR. KARZON: You could even package that epitope differently so that you just have no possibility of

interfering with other systems.

DR. LOBET: By packaging, what do you mean exactly?

DR. KARZON: Delivering it. You take an epitope in itself with the very short peptide chain -- a very limited chain. But you would have to do a variety of things, many of which are currently under study with other vaccines, to make it immunogenetic.

DR. LOBET: As I said, this is confirmation on epitope. So you cannot expect a peptide to mimic this epitope. So you need a structure of the protein to mimic this. That is one thing. The second thing is that apparently this second half of OspA is quite sensitive to any modifications you could make around this. So if you truncated it, you may lose its epitope. So the most likely antigen to use or the most useful antigen to use so far is the full length protein.

CHAIRPERSON FERRIERI: I would like to have two of our consultants go next, and then we may need to close before Lucey's presentation. Dr. Luft and the Dr. Dattwyler. Go ahead, please.

DR. LUFT: In the data regarding the evaluation

for suspected Lyme disease that Allen presented, he said about 1,000 patients self-reported symptoms for Lyme disease, and then in the subsequent year it actually went down to about 690. What happened to these patients? What were their diseases and do they segregate it in any way according to vaccination? And furthermore, why was there this very significant drop in the number of subjects that were self-reporting symptomatology between year one and year two and was this a vaccine effect?

DR. PIETRUSKO: Dr. Sikand will address that question.

DR. SIKAND: We specifically looked at the issue of what did these patients have. Let me back up by saying that we actively solicited any possible symptom of Lyme disease, including arthralgias. And as you are aware or as we are aware, arthralgia can become a very broad symptom in a patient's mind. If I sent a postcard out or spoke with a patient over the telephone about a joint pain, it could be to them something quite different from what we look at as arthralgia or arthritis. Indeed, we brought them in. What were these diagnoses? Very often they were tendinitis, osteoarthritis, bursitis, and various other syndromes relative

to the joint. But in order to be completely certain that we were not missing manifestations of Lyme disease in these subjects, we indeed did acute and convalescent serologies on these patients so as to be sure that we weren't missing manifestations of Lyme disease.

In answer to your question about why there was a significantly smaller number of subjects in year two evaluated according to the same laboratory and symptom criteria, I personally believe, and this is my subjective impression, that the reason is that these patients had already had various aches and pains evaluated in year one and they were reassured that those aches and pains were not Lyme disease. So when they had similar symptoms in year two, they felt a little more comfortable in not calling me and saying that they thought they had Lyme disease.

DR. LUFT: I mean, I asked specifically whether these patients were evaluated as to their vaccine status and whether they segregated in any particular way.

DR. SIKAND: There was no difference between vaccinees and placebos in terms of those particular symptoms. Indeed, the data were presented earlier by Dr. Parenti regarding patients who were presented to the DSMB as having

had symptoms of arthralgia. I believe the symptoms needed to have persisted for longer than approximately a month before they entered that category. And when they were analyzed according to a system of A or B -- i.e., they were not unblinded, they were A or B -- there was no difference between vaccine and placebo in presenting with that symptomatology.

DR. LUFT: Independent of serologic status?

DR. SIKAND: I beg your pardon?

DR. LUFT: Independent of their serologic status?

DR. SIKAND: Serologic for?

DR. LUFT: I mean, did you use the serology to be able to make that assessment as to whether they were Lyme disease or non-Lyme disease?

DR. SIKAND: Serology was indeed used to see whether they had Lyme disease or if they did not have Lyme disease in terms of their work-ups. This is for suspected Lyme disease you are talking about?

DR. LUFT: No. I am just asking whether the 1,000 patients, were they segregated into the vaccine group versus the placebo group. That is all I am asking.

CHAIRPERSON FERRIERI: Could one of you address

that briefly?

DR. PIETRUSKO: Dr. Parenti.

DR. PARENTI: Could you give me slide 38 and 39 in Dr. Steere's carousel, please? What these slides show is the attack rates in the non-cases, and we have separated them into -- again, if you recall, Dr. Steere had described category 0 and category 9, and then we combined them. So category 0 were people who had the complete evaluation. We have all the data and you can make a full assessment. Category 9 was basically a partial evaluation. As you can see -- I am sorry, this is for both years combined. You can see that virtually equal numbers were evaluated for category 0 and category 9. There were slightly more people in the vaccine group overall. Almost 660 versus 613 with a P value of .09.

Interestingly, we went back through these subjects and looked at who might have actually been a sero converter, and if anything there is more potential cases in this group, in the placebo group, than in the vaccine group. So I don't think that we are just having people come in and be evaluated and discounting their symptoms and kind of dumping them into these categories and not counting them as vaccine failures. Is that your point, Dr. Luft? Is that your

question?

DR. LUFT: Yes, for the most part.

DR. PARENTI: The other thing I would just add to Dr. Sikand is Dr. Sikand had the largest number of subjects in this study, but in terms of what did people have as far as their symptoms were concerned, I heard the same thing from other investigators as to year two and why weren't as many people evaluated. I heard this same theme from other investigators. As soon as this study started, people took this as an opportunity to have their vague, long-standing symptoms evaluated and after that was done in year one, they didn't repeat that.

CHAIRPERSON FERRIERI: Do you have another slide, Dr. Parenti, or is that it? That is it?

DR. PARENTI: Yes, I think that makes the point clear.

CHAIRPERSON FERRIERI: Dr. Dattwyler, you had a question.

DR. DATTWYLER: It is along the same lines as Dr. Kaplan's question. OspA has both protective and non-protective epitopes. In the cases of vaccinated individuals who subsequently developed infection, was the LA equivalent

significantly less than the people who were protected? And were there individuals who had reasonable titers of anti-OspA and yet had low titers of the protective LA-2 equivalent?

DR. PIETRUSKO: Okay, the correlation between LA-2, Dr. Parenti will answer that.

DR. PARENTI: The reverse cumulative curve that I previously showed for IgG is virtually exactly the same for LA-2. So if you look at the year one vaccine failures where I had the reverse cumulative curves, the data are virtually the same.

DR. DATTWYLER: But those are means. What I am asking is are there individuals who have reasonable titers of OspA yet do not make enough anti-LA-2 equivalent?

DR. PARENTI: There is an excellent correlation between the two antibodies. We have previously --

DR. DATTWYLER: In all cases?

DR. PARENTI: I can't say it is exactly all cases. I mean, the correlation is very, very tight. If you want to hold on --

DR. DATTWYLER: And then the other question is with repeat immunization, does that still hold true? Because if you look at the LA-2, it is in the carboxy portion of the

molecule where the lipidation site is in the amino portion of the molecule, and that is more -- is there non-protective epitopes which may be more antigenic and therefore with repeated immunizations give you higher and higher titers?

DR. PARENTI: Could you give me overhead number 43 and 44, please?

CHAIRPERSON FERRIERI: This will be the last question that will be answered. I have made note of other members of the committee who want to comment, and we will do that after lunch before we have the presentation of questions. There will be a number of issues that we still need to ask the sponsors. Dr. Parenti, could you address this briefly now, please?

This is a very important question and I would like it addressed at this time, even though it is encroaching on Dr. Lucey's time.

DR. PARENTI: There is actually a series of overheads here. The first one shows a correlation between IgG and LA-2. This is for month two.

CHAIRPERSON FERRIERI: Lights down a bit, please.

DR. PARENTI: I apologize, I don't see the R

value in there. But you can see there is a very good correlation between the two. If you could put the next one up as well. This is at month 13 -- again, one month after the third dose. You see basically the same correlation.

CHAIRPERSON FERRIERI: And these are ELISA units on the X axis?

DR. PARENTI: I am sorry, we have -- this is the IgG ELISA units on this axis and this is the LA-2 on the Y axis. And the third time point that we have is month 20, which is again towards the end of the study and titers have started to fade. If you could put number 45 on, please?

DR. DATTWYLER: There are some outliers there, though. I mean, certain people have higher titers of anti-OspA that don't have high titers of anti-LA-2 on that previous slide.

DR. PARENTI: Right. It is not 100 percent, but generally there is good correlation.

DR. DATTWYLER: I think that is an important point.

DR. PARENTI: And again, a similar pattern at month 20.

CHAIRPERSON FERRIERI: Thank you. I know how

anxious all of you are to get your questions out. They will emerge later. Please don't forget them. Jot them down. We will move to Dr. Dan Lucey from FDA, who will present now. When he is through, we will break for lunch.

DR. PIETRUSKO: Dr. Ferrieri, we have a few conclusion slides.

CHAIRPERSON FERRIERI: Oh, I am sorry. I thought you had concluded. Would you like to do that now?

DR. PIETRUSKO: Not quite. We are almost there.

CHAIRPERSON FERRIERI: Almost? You promise?

DR. PIETRUSKO: It will be only a few minutes.

CHAIRPERSON FERRIERI: Apologies.

DR. PIETRUSKO: That is okay. I will give a few concluding remarks. Thank you, Dr. Ferrieri. In conclusion, Lyme 008 was a prospective, well-designed, randomized, controlled clinical trial. It was a truly remarkable study. Why was it remarkable? For a number of reasons.

First, we had more than 22,000 person years of observation during the study. And as Dr. Parenti mentioned, it is currently ongoing for those who have been involved in

that study that were switched over from placebo and also those patients that were originally randomized to LYMErix vaccine.

Dr. Steere mentioned the impressive subject compliance. It was truly remarkable over this two-year period that there was 95 percent compliance with the visits and follow-up in these individual subjects. There was rigorous subject evaluation for suspected Lyme disease. Over 1,000 cases were evaluated and each case was independently evaluated in a blinded fashion by the data safety monitoring board.

There was a large, unique data base regarding asymptomatic infection based upon the placebo population and the serology that was taken at the time. Serologic evaluation is available with baseline reference. It also provides access to serial epidemiology and there was an extensive and detailed safety data base both with solicited and unsolicited spontaneous adverse events.

You have heard from Dr. Schoen and Dr. Sikand that there is a definite need for such a vaccine against an emerging infection. You have heard from Dr. Lobet about the novel postulated mechanism of action in the mid gut of the tick. You have heard Dr. Steere present the data on the efficaciousness of this particular product as demonstrated in

Lyme 008, and you have heard from Dr. Parenti that this product is highly immunogenic, safe, and well-tolerated.

Based upon these findings, we believe that LYMErix is both safe and effective and will represent an important new public health approach for the prevention of Lyme disease, including asymptomatic infection. Thank you.

CHAIRPERSON FERRIERI: Thank you, Dr. Pietrusko. We will move on then to Dr. Dan Lucey from FDA. Please take the time that you need, Dan, that was allotted. Don't feel that you need to truncate it.

DR. LUCEY: Thank you, Dr. Ferrieri.

CHAIRPERSON FERRIERI: The table has a copy of this presentation to follow.

DR. LUCEY: Good afternoon. Between now and 12:45, I would like to present the FDA's review on safety, efficacy, and immunogenicity of SmithKline Beecham's Lyme disease recombinant OspA vaccine.

First of all, I would like to address the issue of the safety data base. Overall, we have seen data on greater than 18,000 subjects who have received at least one dose of this vaccine. 6,400 subjects ages 15 to 70. Most of these subjects were in the pivotal efficacy trial, Lyme 008.

15,902 vaccine doses were given to 5,469 subjects. In addition, there have been six other clinical trials involving 2,180 doses in 1,009 subjects who received at least one dose of this vaccine. The overall safety data is similar to that seen in the pivotal Phase III study Lyme 008.

As you heard from Dr. Steere, Lyme 008 was a randomized placebo controlled study involving 5,469 vaccinees and 5,467 placebo subjects. The subjects were 15 to 70 years of age. They were vaccinated on a 0, 1, and 12-month schedule, and there was 20 months of blinded follow-up.

With regard to safety monitoring, there was both solicited and unsolicited adverse events. The solicited adverse events were done in a subset according to protocol of 402 vaccinees and 398 placebo subjects. The unsolicited adverse events of course involved all subjects.

Now I would like to present data first on solicited and then later on unsolicited adverse events. This first table shows from Lyme 008 the incidence of solicited local symptoms reported on days 0 to 3 by diary card after each vaccination dose. What I would like to call your attention to here is that for these three local solicited adverse events of redness, soreness, and swelling, there was a

higher incidence in vaccinees compared to placebo. However, I would like to emphasize that going from dose one to dose two to dose three, there was no increase in the frequency of adverse events in vaccinees.

Next with regard to the incidence of solicited systemic symptoms, again reported on days 0 through 3 by diary card after each vaccine dose, you will see that as the sponsor earlier pointed out, there was a statistically significant increase in arthralgias, fatigue, and rash, that is, a higher frequency in vaccinees compared with placebo, and not for headache or fever. But again, going from dose one to dose two to dose three, there was no increase in the frequency of adverse events in the vaccinees.

Moving now to the incidence of specific unsolicited adverse events occurring at a frequency of at least 1% percent within 30 days post-vaccination. This involves all subjects. It is intention-to-treat. You will see that the vaccinees had a higher frequency of injection site pain and injection site reactions, fever, influenza-like symptoms, myalgias, and rigors. There was no difference between vaccinees and placebo subjects in terms of arthralgias or rash. And I would like to add that this table focuses on

frequencies of at least one percent. Arthritis occurred in both groups, vaccinees and placebo, at a frequency of less than one percent. And specifically it was 0.9 percent in vaccinees and 0.8 percent in placebo subjects. So there was no difference in arthritis within the first 30 days of vaccination.

Moving now to unsolicited adverse events, again occurring at a frequency of at least one percent at greater than 30 days post-vaccination for all subjects. Here you will see that there were NSs for not significant. There was no statistically significant differences between vaccinees and placebo for any of the unsolicited adverse events which we showed on the previous slide, and those specifically include arthralgias and arthritis and tendinitis.

Looking now specifically at the incidence of unsolicited musculoskeletal system disorders, and that included not only joint but also bone and muscle abnormalities under the rubric of musculoskeletal system disorders. For all subjects less than 30 days post-vaccination on the top panel and greater than 30 days post-vaccination on the bottom panel. What you will see is that there was a statistically significant difference within 30 days post-vaccination, such

that vaccinees had a higher frequency of unsolicited musculoskeletal system disorders than did the placebo subjects. At greater than 30 days post-vaccination, there was no statistically significant difference between vaccinees and placebo.

I am sorry you can't see the top of this slide. This is the frequency of serious adverse events following any vaccine dose by body system. Here you will see numerous body systems listed on the far left part of this slide. You will note that again NS stands for not significant. There were no statistically significant differences between vaccinees and placebo for any of these multiple body systems, with one exception, metabolic and nutritional, where placebo had a statistically significant higher frequency, .13 versus 0 in the vaccinees.

In particular, musculoskeletal system disorders is included in this table as are central and peripheral nervous system abnormalities and autonomic nervous system abnormalities, psychiatric and gastrointestinal as well as cardiovascular and myocardial, endocardial, and pericardial and valve abnormalities.

With regard to deaths in Lyme 008, there were

15 deaths total. None, as was mentioned by the sponsor, are attributed to the vaccine. There were 10 deaths in the vaccinees and 5 in the placebo. There was a total of six cancers, 5 in the vaccinees and one in the placebo. There were 5 myocardial infarctions, MIs, or probable myocardial infarctions, MIs, 4 in the vaccine group and 2 in the placebo. In the placebo group, there was one subject who had sudden death and one subject who had septic shock and one subject who died of stabbing.

Again, as has already been mentioned, in the 1994 and to some extent in the following 1996 Vaccine Advisory Committee Meeting, there were three theoretical safety concerns raised with regard to vaccination with this OspA protein.

First was to assess the safety of vaccination in individuals who report a history of Lyme disease or have a positive Western blot to Borrelia burgdorferi prior to vaccination.

The second is to assess the effect of vaccination on the temporal onset and clinical manifestations of Lyme disease.

The third was the occurrence of arthritis in

study participants, in particular would vaccination with OspA induce autoimmune arthritis?

Taking this first safety concern, that is, to assess the safety of the vaccination in individuals who report a history of Lyme disease or have a positive Western blot to Borrelia burgdorferi, data from Lyme 008, specifically the incidence of unsolicited adverse events reported within 30 days post-vaccination for subjects with a history of Lyme disease, there was a statistically significant difference in local reactions such that vaccinees had more than placebo. However, there is no difference in systemic adverse events. So this is similar to what was seen with regard to all the enrollees in Lyme 008, that is, a higher frequency in vaccinees than placebo of local adverse events occurring within 30 days of vaccination.

Looking now at the incidence of unsolicited musculoskeletal system disorder for subjects with a history of Lyme disease. Again, the top panel is for less than 30 days post-vaccination and the bottom panel is for greater than 30 days post-vaccination. You will see that there was a statistically significant difference at less than 30 days post-vaccination such that vaccinees had a higher incidence of

unsolicited musculoskeletal system disorders than did the placebo subjects. However, at 30 days post-vaccination, there was no difference between the two groups.

Turning now to persons who had a positive Western blot at baseline. And again, looking at incidents of unsolicited adverse events reported within 30 days post-vaccination for subjects with a positive Western blot. Again, there was a statistically significant difference for local but not systemic adverse events, such that vaccinees had more local adverse events than did the placebos.

Again now moving on to incidence of unsolicited musculoskeletal system disorders for subjects with a positive Western blot at baseline. Again, the top panel shows less than or equal to 30 days post-vaccination data and the bottom panel greater than 30 days post-vaccination data. You will see that in this group of people who had a positive Western blot at baseline, there was no statistically significant difference between vaccinees and placebo either at less than 30 days post-vaccination or greater than 30 days post-vaccination with regard to unsolicited musculoskeletal system disorders.

The second theoretical safety concern is that

of the effect of vaccination on temporal onset and clinical manifestations in individuals who develop Lyme disease. There are three points that we would like to make in this regard, that is, the effect of vaccination on the clinical manifestations of Lyme disease in this study, Lyme 008. The majority of cases in both groups presented with erythema migrans, EM, in both years, year 1 and year 2, as has been discussed and presented earlier this morning. The onset and the duration of erythema migrans did not differ between groups. Again, that was true for year 1 and year 2, and the data has previously been shown. The proportion of cases diagnosed by culture, PCR, for Borrelia burgdorferi or Western blot for Borrelia burgdorferi was comparable between the two groups.

This table shows from Lyme 008, the month of onset, for category 1 cases, that is, definite Lyme disease, in year one according-to-protocol or ATP. You will see the column on the left is the month in which the subject in the study was diagnosed, the vaccine, number and the percent of cases, and placebo, the number and the percent. What we would like to emphasize is that nearly all persons diagnosed with Lyme disease, both in the vaccine group and the placebo group,

presented and were diagnosed in either June, July, or August. I think there was only one person in the first year who was diagnosed after the end of August, and that was in September. The year two data is essentially the same, that is, no difference between the temporal onset of Lyme disease in vaccinees and placebo subjects.

The third theoretical safety concern that was raised in the 1994 Vaccine Advisory Committee was that of the occurrence of arthritis in vaccine study participants, specifically could OspA vaccination induce an autoimmune arthritis. As has been mentioned, there are several ways of looking at this data, and after this slide I would like to show a couple of overheads before moving on to additional slides.

First of all, in the intention-to-treat analysis for Lyme 008, looking at arthritis as a serious adverse event after any vaccine dose, the number of vaccinees and the number of placebo subjects was identical, that is, five in each group for a frequency of 0.1 percent in each group. Again as has been mentioned, the data safety monitoring board analysis looked at both year one and year two to see if there was any evidence of an increased frequency of

arthritis in vaccinees. In year one, there were a total of 107 subjects who had symptoms that were attributable at all to arthralgia that occurred within 30 days after vaccination and that persisted for at least 30 days. The DSMB did a blinded comparison -- an A versus B comparison -- and found no difference between vaccinees and placebo, that is, the number of vaccinees and the number of placebo in this group of 107 were identical. They were broken down in several ways. One was arthritis/tendinitis and another was alternative diagnosis and that could include fibromyalgia or over-use syndrome or other diagnoses. An additional group were people who had a totally normal physical exam performed by a physician. So there was no difference in year one between vaccinees and placebo in the 107 people that had symptoms that either were or sounded like arthralgias that persisted for at least 30 days after or occurring within the first month after vaccination.

Then looking at year one and year two, there was a total of 304 persons who had an evaluation because of any adverse event that sounded like an arthritis. Again, there was no evidence of increased frequency of arthritis after vaccination. That was the DSMB analysis that was done

separately by three members of the DSMB and then analyzed by the DSMB statistician independently. There are no differences found between the vaccinees and placebo for any of the three individual independent DSMB member evaluations.

If we could have the overhead now?

DR. FLEMING: Are you going to show us the treatment breakdowns? Are you showing how that broke down by group?

DR. LUCEY: I do have an overhead that I can show for the year one 107. I have broken them down into vaccine and placebo, specific ones. Here we would like to show just a couple of overheads. This is fairly recent data that has come to light and has been addressed by Dr. Steere and Dr. Parenti in their presentations.

I want to emphasize first of all that up until now I have been talking about vaccinees, Lyme 008 in particular. This overhead addresses not vaccinees but patients with treatment resistant Lyme arthritis. This is to set the context. Again, Dr. Steere has already presented this and Dr. Parenti has amplified it. But I would like to start with this overhead that focuses on treatment resistant Lyme arthritis, not vaccinees.

There has been found an increased frequency of certain HLA DR alleles compared to treatment responsive Lyme arthritis. There has been found an increased T cell proliferation to certain outer surface protein A peptides -- what has been referred to as peptide 8 -- compared to treatment responsive Lyme arthritis. Dr. Steere and colleagues have found a homologous amino acid sequence identified between one of these OspA peptides and the human protein lymphocyte function antigen 1 or LFA-1. And he showed where the amino acid homology was located, between OspA amino acids 165 to 173, and LFA-1 I believe is amino acids 332 to 340. In addition, LFA-1 induces T helper cell reactivity as determined by gamma Interferon production in 9 out of 11 patients who have treatment resistant Lyme arthritis. So that is the context looking at patients, not vaccinees, with treatment resistant Lyme arthritis.

With regard to Lyme 008 -- so moving now back to the vaccinees and to the study Lyme 008, the Phase III study. There was a cell mediated immunity subset, or as we heard earlier this morning in a sense two subsets. This was the main one of 100 consecutively enrolled study subjects from one study site. So this was independent of any symptoms.

Simply consecutively enrolled subjects. Of the vaccinees and placebo, there were 41 vaccinees and 44 placebo who had viable cells after the cells were thawed. They were frozen, drawn two weeks post third dose. And when they were thawed, there were viable cells for evaluation in 41 vaccinees and 44 placebo subjects. The T cell responses were measured to full length OspA and SKB and OspA peptides, including the peptide 8 which shares the homology with LFA-1. HLA typing has so far been completed on 40 vaccinees but no placebo subjects. So in a sense, this work is still in progress and that work on HLA typing of the placebos is ongoing I understand.

What we know about the vaccinees from this CMI subset from one study site are that T cell responses to full length OspA and OspA peptide 8, that is, the peptide that contains the amino acid sequence homologous to LFA-1, were detected in peripheral blood lymphocytes or PBLs in a subset of vaccinees. Preliminary data suggests that T cells from vaccinees with certain HLA DR alleles had greater reactivity to full length OspA and to OspA peptide 8. T cell responses to LFA-1 in vaccinees have not been studied.

In this overhead I would like to present some data that I believe Dr. Steere has presented perhaps in a

graphic form. This is in text form. T cell responses to full length OspA and then in the lower panel to OspA peptide 8. So in the upper panel, T cell responses to full length OspA by proliferation assay, that is, T cell proliferation, were found in, as I mentioned, a subset, that is, 13 of 41 vaccinees. So about one-third of vaccinees had T cells that proliferated in-vitro to full length OspA. Versus only one out of 44 placebo subjects.

Another read-out was gamma Interferon production in culture supernatant and this was assayed by ELISA. Here 2 out of 39 vaccinees versus 0 out of 24 placebo subjects were studied. And again, you will note that only 24 placebo subjects have been studied so far. So again that is work that I understand is still in progress to study the remainder of the placebo subjects.

T cell responses in the lower panel to OspA peptide 8. Again, the proliferation assay, 9 out of 41 vaccinees produced gamma Interferon in-vitro -- I am sorry, 9 out of 41 vaccinees proliferated -- T cells proliferated in-vitro to OspA peptide 8 versus only 2 out of 44 placebo subjects. Gamma Interferon production in the culture supernatant, 2 out of 39 in the vaccinees versus 1 out of 24

placebo subjects produced gamma Interferon in-vitro.

The final overhead that we have is fairly detailed and I will go through it. This is the patient that Dr. Steere described to us in some detail. There is one point at the end that I think bears mentioning for completeness sake if no other reason. That is the subject was a 61-year-old woman who is the only vaccinee in the cell mediated immunity subset with high gamma Interferon levels when stimulated with OspA peptide 8. This subject had HLA typing performed and it did reveal HLA DR-4 allele, particularly one that is associated with so-called rheumatoid arthritis allele. It is associated with the ability to present the OspA peptide in question. This subject received dose 1 and dose 2 in March and April of 1995 respectively. Arthralgias began one day after the second dose, specifically pain in the left shoulder, elbow, and wrist. It was unresponsive to non-steroidal anti-inflammatory drugs and steroid injection and persisted for at least three months. Paresthesias also occurred beginning one week after the second dose. Numbness and tingling in the fourth and fifth fingers. Nerve conduction studies were normal and these symptoms eventually resolved in April of 1996, that is, the paresthesias. The patient was evaluated

for Borrelia burgdorferi infection and the serology was negative. The subject did have the third dose in February of 1996 while the paresthesias were still present. However, the patient had no recurrence of her arthralgias and she had no worsening of her paresthesias.

In May of 1997, that is, 15 months after the third dose of vaccine given in April of 1996 -- in May of 1997, the patient was hospitalized with acute renal failure. It was of unknown etiology. It did require dialysis. However, then her renal function returned to normal. In speaking with the sponsor, the patient was evaluated for the etiology of her renal failure. To our knowledge, no renal biopsy was performed. However, no etiology was determined for her renal failure occurring 15 months after her third dose of vaccine.

Now I would like to continue with the slides. In concluding the safety portion of this presentation, we would like to emphasize that from Lyme 008, there is limited safety data for several specific groups. Number one, subjects who are 15 to 18 years of age. We have seen data on 151 or 152 vaccinees, only 3 of whom were in the solicited adverse event subset. But otherwise, the safety data base appears

similar to vaccinees who are greater than 18 years of age for unsolicited adverse events. Subjects greater than 70 years of age were excluded from Lyme 008, so we don't have data for safety or efficacy there from Lyme 008. Subjects with a history of chronic joint or neurologic illness related to Lyme disease or second or third degree AV block or with cardiac pacemakers were also excluded from the study, and subjects with a history of chronic joint disease due to other etiologies -- while this was not an exclusion criteria, it is unclear to what extent such subjects were enrolled in the study.

I would like to move now to efficacy analysis. I won't dwell excessively in areas that have already been presented. According-to-protocol analysis versus intention-to-treat analysis -- again in according-to-protocol year one involved all subjects starting four weeks post-second dose through month 12, and this was the primary cohort for analysis. Year two, all subjects starting immediately post-dose three through month 20. This was the secondary cohort for analysis.

The intention-to-treat involved all subjects who received at least one dose of vaccine or placebo, and this

was the secondary cohort for analysis. The primary efficacy endpoint for according-to-protocol, ATP, was definite Lyme disease category 1 in the first year of the study between four weeks following the second dose of vaccine and month 12. As has been defined, category 1 was definite Lyme disease requiring any of these four clinical manifestations, classic clinical manifestations of infection with Borrelia burgdorferi, and at least one of the following laboratory confirmations, that is, either Western blot, PCR, or culture.

To emphasize, erythema migrans had to be physician diagnosed, photographed, measured with a ruler and biopsied. The biopsy was split into two and half went for culture for Borrelia burgdorferi and half went for PCR for Borrelia burgdorferi.

Category 2, possible Lyme disease. There are really subjects in only category 2.1 and 2.2. There is no one in 2.1, so I won't dwell on that. 2.2 is erythema migrans of at least 5 cm in size but in whom the laboratory tests were performed and were negative. In category 2.2, flu-like illness with a Western blot sero conversion to Borrelia burgdorferi. Category 3, as mentioned, is laboratory confirmed asymptomatic infection with Borrelia burgdorferi and

here it involves sero conversion by Western blot IgG on prepared sera for year one or year two.

Inclusion criteria, just to emphasize, is healthy subjects ages 15 to 70 who are at risk of acquiring Lyme disease because of where they reside or if they had frequent outdoor activities in high risk Lyme disease endemic areas.

Selected exclusion criteria included physician diagnosed, chronic joint or neurologic illness related to Lyme disease, current disease associated with joint swelling, diffuse joint or muscular pain, Lyme disease treated with antibiotics within three months and known high degree AV block or pacemaker.

This is the efficacy data for year 1. Vaccine efficacy per according-to-protocol analysis. Here we seen in the fallet categories 1, 2, and 3, vaccine versus placebo vaccine efficacy, point estimates and 95 percent confidence intervals. For definite Lyme disease, category 1, 20 cases in vaccinees versus 40 in placebo in year one to give a vaccine efficacy point estimate of 50 percent with a lower bound in the 95 percent confidence interval of 14 percent. Category 2, there was no statistically significant difference between

vaccinees and placebo with a vaccine efficacy estimate of 21 percent. Category 3, asymptomatic sero conversion, two cases in vaccinees and 12 in placebo. Vaccine efficacy estimate of 83 percent with a lower bound in the 95 confidence interval of 25 percent.

For year two, again according-to-protocol analysis, same format. For category 1 definite Lyme disease, there were 13 cases in vaccinees versus 61 in placebo, yielding a vaccine efficacy estimate of 79 percent with a lower bound of 61 percent. Again for category 2, possible Lyme disease, there is no statistically significant difference. And for category 3, asymptomatic sero conversion, there were no vaccinees and 13 placebo subjects with a point estimate of 100 percent vaccine efficacy and a lower bound of 30 percent.

The intention-to-treat analysis, as has been mentioned, was very similar to according-to-protocol both for year one and year two. I will show that just briefly on the next two slides. For category 1, 22 cases in vaccinees and 43 in placebo. The estimate of vaccine efficacy is 49 percent with a lower bound of 15 percent. Very similar to the according-to-protocol analysis.

For year two ITT analysis, again very similar to according-to-protocol. So looking just at category 1 for example, 16 cases in vaccinees and 66 in placebo. The point estimate is 76 percent with a lower bound of 58 percent.

On this slide, we would like to emphasize that in Lyme 008, vaccine efficacy for category 2.2 -- and again that is asymptomatic Western blot sero conversion -- and category 3, which is asymptomatic sero conversion, again requiring Western blot sero conversion. So both category 2.2 and category 3 required Western blot sero conversion. Category 2.2 required flu-like symptoms. Category 3 required the absence of symptoms.

Looking at vaccinees versus placebo for category 2.2 in year one, again there was no statistically significant difference for category 2.2 comparing vaccinees and placebo. The vaccine efficacy point estimate is 20 percent. For category 3, as has been shown, there was a statistically significant difference. 83 percent was the point estimate for vaccine efficacy for category 3. Similarly in year two for category 2.2, there is no statistically significant difference between vaccines and placebo. The point estimate was 50 percent. And for category 3,

symptomatic sero conversion, the point estimate was 100 percent with a lower bound of 30 percent.

Moving to the final topic now, immunogenicity subset results. This involves, as has been mentioned by Dr. Parenti, the Center 24 vaccinees. This was the immunogenicity subset in Lyme 008. This table is very similar to the one that Dr. Parenti presented already. What you will see is the time at which the vaccine was given, the number of subjects, the geometric mean titers of total anti-OspA IgG in ELISA units per ml, and the final column on the right is the percent of sero positivity which was defined as at least 20 ELISA units per ml. What you will see is that at post-dose 2, that is, at month 2 in the study, the GMT was 1,239 and 99 percent of vaccinees were sero positive. By pre-dose 3, that is, month 12, the GMT had declined by more than one log to 117 with 86 percent of vaccinees now being sero positive. Post-dose 3, which was given at month 12 -- so now one month after post-dose 3, that is, at month 13, the GMTs were now up to 6,033 and 100 percent of vaccinees were sero positive. And looking out now at month 20, that is, 8 months after the third dose, GMTs had declined to 1,997 and sero positivity rate was 98 percent.

In this figure which shows on the y axis the IgG anti-OspA GMT and on the x axis the month of the study starting at month 2 and continuing out to month 21, what are plotted are the time course of IgG anti-OspA antibody titers in vaccinees -- again, vaccinated on the Lyme 008 schedule of 0,1, and 12 months. What you will see are antibody titers for two control groups. One, the GMTs for Center 24, abbreviated C24, and the 95 percent confidence intervals. That is this simple: Center 24 had anti-OspA titers measured at four time points -- time zero, which is shown here. You can see the titers are approximately 1,200, which is what we saw in the previous table. And then at month 12 here, where the titers are approximately 117, as you saw in the previous table. And then at month 13, where the titers have gone up to about 6,000. And then at month 20, where they have come down to about 2,000. In-between what you see plotted in the solid lines connected by the solid dots are the GMTs for the category zero subjects, that is the subjects that were discussed earlier who were evaluated for possible Lyme disease but were ruled out for Lyme disease, both by physical exam and by laboratory test. Of course these category zero subjects could present at any time during the year, so we have antibody

titers throughout year one and then throughout year two. The dotted lines are the 95 percent confidence intervals around the GMTs here for the category zero subjects.

What I would like to emphasize is that in year one of the study, nearly all cases of acute Lyme disease occurred by month 6 -- right here, by month 6 of the study. In fact, nearly all of them occurred between month 3 and month 6. As I showed you earlier, essentially in the summer -- June, July, August. So what I would like to call your attention to is that at month 6 or by month 6, at which time all the cases of acute Lyme had occurred during year one, the antibody titers, which is the measurement that we have of the immune response as a whole for the vaccinees, had declined to this level from where they had started originally. They continued to decline, as we know, during the rest of the year prior to the third dose at month 12. And it is during this time, after month 6 or between month 6 and month 12, when the antibody titers continued to decline that there was essentially no cases of acute Lyme disease. And that is most likely due to the fact that the tick season, and therefore the transmission of Borrelia burgdorferi season had passed. So we don't know about the effectiveness of the immune response

represented here by antibody titers against OspA against acute infection with Borrelia burgdorferi. Because there were no ticks and therefore no risk of transmission of Borrelia burgdorferi. The pattern in year two was essentially the same, but for brevity's sake, I emphasize year one.

So with regard to seasonality of vaccination, there are several issues that we would ask you to consider. And again to reiterate, essentially all the cases of category 1 occurred in the first year by month 6 and the pattern was similar in year two. Anti-OspA IgG antibody titer is lowest between month 7 and month 12, as shown in the previous figure, when the season for tick transmission of the spirochete, Borrelia burgdorferi, is over. The efficacy of the vaccine given just before the Borrelia burgdorferi transmission season, as was done in Lyme 008, has been estimated and has been shown. However, the efficacy of the vaccine when given at other times with respect to this transmission season of Borrelia burgdorferi is unknown.

Finally I would like to close by emphasizing again what Dr. Parenti has presented, and that is that there are additional studies ongoing. These include longer term follow-up. Approximately 1,600 vaccinees from Lyme 008 have

been followed for ran additional 12 months so that they have a total of 36 months after their first vaccination for follow-up and evaluation. Persistence of antibody and the effect of a boosted dose is being evaluated in approximately 350 Lyme 008 vaccinees who were immunized at month 24 after getting three doses at time 0, 1, and 12 months. And at month 24, half were given vaccine and half were given placebo. So 175 in each arm. Alternate schedules of vaccination are being studied, specifically 0, 1, and 6 months is being compared with 0, 1, and 12 months. And 0, 1, 2, and 12 months is being compared with 0, 1, and 12 months. And finally, the pediatric population is also being studied. Thank you very much.

CHAIRPERSON FERRIERI: Thank you, Dr. Lucey. I would like the panel to hold their questions until after lunch. Please jot them down. We will adjourn now unless Mrs. Cherry has any announcements. Just one second, please.

MS. CHERRY: Just one very minor thing. Is there a Dennis Dixon in the group? I have a message for you.

CHAIRPERSON FERRIERI: Thank you, Nancy. We will reconvene then in one hour, approximately 1:55. Thank you.

(Whereupon, the meeting was adjourned for lunch

at 12:53 p.m. to reconvene this same day at 2:00 p.m.)

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

2:00 p.m.

CHAIRPERSON FERRIERI: I'd like to call the afternoon meeting to order. We will start the afternoon session with the open public hearing. And then as I indicated, we will be reopening questions for the sponsor and FDA. If you could just be patient a few seconds, Ms. Cherry, our Executive Secretary, will open up the public hearing. May we have your attention, please? There is only one show going on.

MS. CHERRY: At this time, I have three letters that I received. Unless the individuals are in the audience, I will read the letters.

The first is Anne Hirschberg from Cleveland, Ohio. This is the letter I received dated May 9. "Here is my opinion and commentary on the proposed vaccines for Lyme disease being discussed at the May 26-27 meeting of the FDA Vaccines and Related Biological Products Advisory Committee. Thank you for allowing my input on this matter. Until there is an infallible test for Lyme disease proving that the person getting the vaccine does not already have the disease, it is too dangerous to give a Lyme disease vaccine to anyone. The

effects of a vaccine on those already infected has not been discussed. I am also concerned that the vaccine would mask the early symptoms and lead to sero negative and chronic cases of Lyme disease. Until there is a vaccine which covers all the strains of the organism and all the protein coatings of same, and which is proven effective and safe for all ages, I will not take the vaccine. Since Lyme disease is not known to be contagious, it would be very difficult to require this hypothetical perfect vaccine for children entering school. I believe the option for vaccination would have to be between the patient and the doctor or between the parent and the doctor in the case of children. The corporate decision as to whether workers should have a vaccination for Lyme disease would have to be worked out between employer and employees. I fear the Lyme disease vaccine would lull people into believing that they are protected against all tick-borne disease when they are concurrently at risk for such diseases as human granulocytic Ehrlichiosis, Babesiosis, and Rocky Mountain Fever, which may be passed on by the same ticks that carry Lyme disease. In my opinion, we do not know how hyperendemic some areas are because the disease is under-diagnosed and under-reported presently. Since the vector can be carried in

any area by a migrating bird or a wandering mouse or deer, the scope of those at risk is more widely spread than has been theorized. Until we have a reliable test for the disease, vaccination is too dangerous. Thank you. Anne Hirschberg, Cleveland, Ohio."

The second letter was from Carole Osborne of West Lake, Ohio. Is Carole Osborne here? Okay. "Dear Sirs, I would like to offer my opinion and concern regarding the Lyme vaccine. What happens to the already infected person that may not know they have Lyme? Two, there are no perfect Lyme tests. No one would know for sure if they have been exposed. Three, the vaccine was tested only for a few of the Lyme strains, what about the others? Four, I am afraid it will lull people into being careless outdoors. Five, what will the requirements be by schools and corporations in the epidemic area? Six, will boosters be required? Will people actually follow-up? Seven, what about all the other tick-borne diseases? I am very fearful of this vaccine and do not feel enough research has been done. I am also very concerned of the doctors involved in the drug study. Thank you for your attention of my concerns. Carole Osborne, West Lake, Ohio."

The third letter was from Ed Lewis of Garrison,

New York. Ed Lewis, are you here? Okay. This is to Ms. Nancy Cherry. Subject line is Vaccine. From the "Silent Majority." "I received the SmithKline Lyme vaccine along with thousands of others. All volunteers who I encountered suffered no problems. I am glad that I volunteered even though I have read the doom and gloom Internet stories of the possible failure of the vaccine. The Web people are likely sending you thousands of messages telling you not to approve the vaccine since the Web nuts are advertising to stop the vaccine. Most of their gripes are about MD's not detecting Lyme early enough to treat it before it caused apparent irreversible problems. We volunteers were not a bunch of ignorant street people. I am an electrical engineer who retired from Consumer Reports testing labs. We were trained to criticize after examining the facts without letting preconceived thoughts interfere. All of the other volunteers who I met seemed to be very intelligent people. I suggest that you approve a one million person Lyme vaccine test. There are enough of us to accept the possible dangers because of the horrible results of acquiring Lyme disease and not being cured early. I bet that if you asked the majority of people with Lyme disease who were late in detection of Lyme

and have developed horrible Lyme disease symptoms that they would have tried the vaccine if these long-term Lyme sufferers could turn back the clocks to before they were infected. These sufferers would elect to take the chance of receiving the vaccine. Please do not let the crowd stop the progress that has already been achieved. Warn the one million volunteers that there might be problems. You will easily get a million volunteers. The polio vaccine had its problems and there are many theories among scientists who would have prevented polio vaccine and many other vaccines from being released if they could have stopped these obviously good vaccines. Sincerely, Ed Lewis."

Is there anyone else in the audience that would like to make a statement? If not, we will proceed with the meeting.

CHAIRPERSON FERRIERI: Thank you very much, Ms. Cherry. We are grateful for letters of this kind and they are real letters in case any of you had any doubt.

MS. CHERRY: Yes, they are.

CHAIRPERSON FERRIERI: I have absolute confidence that CBER/FDA would not ever fabricate letters. In their way, these letters raise wonderful points that are

highly sophisticated actually.

What we will do now is to pursue the questions that did not get a chance before lunch. I would like the sponsors and FDA to be prepared to respond and to be a succinct as possible. Dr. Edwards, you are first on my list if you still have a question. And if you could indicate to whom you want this addressed.

DR. EDWARDS: There was a slide that discussed data that had been compiled in 5 to 15-year-old children. It said that the study was completed. And I wondered if there could be some discussion of the serology, immunogenicity, and safety of that completed trial.

CHAIRPERSON FERRIERI: While this is taking place--

DR. PIETRUSKO: Dr. Parenti will answer that question.

CHAIRPERSON FERRIERI: Thank you. The following people might get their questions ready. Clements-Mann, Dr. Hall, Dr. Kohl, Dr. Daum. And then I will ask Dr. Fleming to restate a question that we have some data available. Dr. Parenti?

DR. PARENTI: This was a trial of 250 children

age 5 to 15 that received vaccination on a 0, 1, 2 schedule. Half of the subjects received 30 mcg and half of the subjects received 15 mcg. And just as a form of summary data, there was no increase in incidence with subsequent injection of any adverse event over the three doses that they received. The only related unsolicited adverse events were again local injection site reactions. There were no related SAE's and there were no hypersensitivity reactions. The vaccine was very well tolerated by these children.

I should mention -- I don't have the specific GMTs, but the children had a much better immune response than adults did.

CHAIRPERSON FERRIERI: Thank you. Dr. Clements -- yes?

DR. ELKINS: It bears mentioning that the study just referred to was a non-IND study done in the Czech Republic and not a US IND study.

CHAIRPERSON FERRIERI: Thanks, Dr. Elkins. Dr. Mary Lou Clements-Mann?

DR. CLEMENTS-MANN: Yes. I was wondering since the efficacy study included people up to 70 years of age, I was wondering if you had any -- I am not aware of the

immunogenicity data in say people over the age of 60 or even 50, but is there an age-related immune response?

DR. PIETRUSKO: Dr. Parenti will answer that question. I believe he has an overhead on that one also.

CHAIRPERSON FERRIERI: We appreciate your being so well-prepared.

DR. CLEMENTS-MANN: Could I just ask while we are waiting for that. In the people that turned out to be break-through cases who had lower levels of antibody, was there any indication that they were in an older age group, as an example, that might not have responded as well?

DR. PIETRUSKO: He also will address that.

DR. PARENTI: This is an overhead. I don't know how well you can see the numbers, but I will walk you through this. We did look at GMT's by age and we looked at it by decade. Let me tell you the bottom line here. The bottom line is that statistically there is no evidence of decreased immune response by age. So here we have 15 to 30-year-olds and then by decade. As expected, numerically the numbers are slightly lower in the older group. But statistically, if you apply statistical analyses across the board, there is no statistical evidence of decreasing titer with age. And again,

that goes for each of the four time points that we looked at.

And I am sorry, your second question?

DR. CLEMENTS-MANN: My second question is about the break-through cases, whether they were of any particular age group. I think initially you said there was no difference by age, but did they cluster more in an older age group?

DR. PARENTI: Statistically there was no difference by age. During year one, the subjects who were over 60, for example, were the same in both groups. In year two, however, we did notice that there were more subjects in the 65 to 70-year-old age group in year two who had broken through. We initially looked at that because we thought that there might be this kind of as-expected immune response in older people that you see with vaccine. But we didn't see it in year one, where interestingly you might actually have thought that you would see it because people generally have lower titers. But we did see it in year two. We subsequently looked at those -- I believe it is six people who are over the age of 65 who were vaccine failures, and it turns out that four out of the six essentially were non-responders right from the first two doses and had minimal if any response to the third dose. The other two had I think lower than average

response to the first two doses. So that group as a whole appeared to be non-responders, but they don't appear to be representative of the elderly as a whole. They don't appear to be representative of the 65-year-olds. Because even over here after two doses, 98 percent of the subjects in the 60 to 70-year-old group were responders.

CHAIRPERSON FERRIERI: We have a burning corollary to this. Dr. Broome?

DR. BROOME: Yes, just a clarification. You said there was no statistically significant difference by age, but did you look at the hypothesis that Mary Lou is proposing that those over 60 had a poorer response as one might biologically postulate?

DR. PARENTI: Again, I can tell you how the statisticians approached it. Perhaps one of them can give me some help right now. Dr. Sennewald?

DR. SENNEWALD: Can you please repeat the question?

DR. BROOME: The question is if you look at the group over 60 compared to under 60, is there a statistically significant difference in the post -- the two-month blood or -- the two month blood?

DR. SENNEWALD: No.

CHAIRPERSON FERRIERI: Excuse me, would you give your name and origin?

DR. SENNEWALD: Dr. Sennewald from Kendall GMI in Munich. The confidence intervals are overlapping, so there is no statistically significant difference between the --

DR. FLEMING: I mean, the confidence intervals could be overlapping and it still could be statistically significantly different. Were you doing any kind of a trend analysis by age?

DR. SENNEWALD: We did a correlation analysis by age and we had correlation coefficients from about 0.1, which were almost not statistically different. The P values were almost about 5 percent. It was just for -- I think that is -- for LA-2, we had at month two a statistically significant trend in age, but not in any other group.

DR. PARENTI: And that was at one time point only, if I recall.

DR. SENNEWALD: Yes, only at one time point. And as I said, the correlation coefficient was 0.1.

CHAIRPERSON FERRIERI: What is your reaction to that, Dr. Fleming?

DR. FLEMING: Well, looking at the data, it is obviously difficult to figure in the variability. There will be obviously with these GMTs a lot of variability.

DR. SENNEWALD: Yes.

DR. FLEMING: So I always have to caution that comment because I can't see the variability in the slides. But there certainly is a real pattern here that I would have anticipated would have shown up statistically. Where, as Claire says, particularly when you note the 60 to 70. But even throughout there definitely does seem to be a pattern in the GMT's that seems age-related. So I am a little surprised, but I have to say I can't see the variability in your data, which could be clouding the significance.

CHAIRPERSON FERRIERI: Thank you. We will move ahead. Dr. Hall, do you still have a question?

DR. HALL: Yes. If I may ask Dr. Steere, please. I am Caroline Hall. If I may ask Dr. Steere, am I understanding that a possible explanation for conundrum between the vaccine efficacy difference in category 2 and category 3 could be Ehrlichia infection? And if so, how does that explain the difference in category 2.1?

DR. STEERE: Well, I think the explanation is

different. Category 2.1 was physician-diagnosed erythema migrans without laboratory confirmation.

DR. HALL: Excuse me. Does that mean that they took the lab test but it was not confirmed?

DR. STEERE: Yes, and they were all negative.

DR. HALL: That doesn't mean nothing was known either way?

DR. STEERE: No. It means the former. The laboratory tests were done and they were all negative.

DR. HALL: Oh, okay.

DR. STEERE: So the physician set I think is erythema migrans. The laboratory test said negative. I think that the explanation for that is that erythema migrans often has the characteristic clinical appearance, but not always. And therefore there is the potential for misdiagnosis of that skin lesion without laboratory data. And that would be my explanation.

With category 2.2, which was flu-like illness with sero conversion, yes I think that the Ehrlichia, particularly the Ehrlichia infection, was the confounding variable. The same tick may transmit both Ehrlichia and Borrelia burgdorferi, and for the moment let me stay with just

those two infectious agents. And that they both may cause flu-like symptoms. And we also know that Ehrlichia infection alone can give one a false positive Western blot for Lyme disease. We determined Ehrlichia titers as well in that group of people as well as looked at PCR results of blood, and anyone who had evidence of co-infection, we excluded and did a subgroup analysis where they only had evidence of flu-like symptoms and Borrelia burgdorferi infection. In that group in year two, vaccine efficacy was just as good as it was for definite cases.

DR. HALL: Thank you.

CHAIRPERSON FERRIERI: Dr. Steere, I would like to pursue that point. You indicated that you had data for Ehrlichia and Babesia, and I wondered if you had that data for category 3 to explain -- the subquestion of this is that there is information to support the IgM reactions in people who may be simultaneously or who may be infected with Ehrlichia. But you stated that IgG may be positive for Borrelia burgdorferi as well?

DR. STEERE: I think it can be, though it is not as clear. And if you ask me what bands you may see in both infections, I couldn't answer the question. We have --

but in answer to your question, we have not done yet the similar study in asymptomatic infection.

CHAIRPERSON FERRIERI: Okay. Fine.

DR. PIETRUSKO: Do you have some additional information?

CHAIRPERSON FERRIERI: We would like to see that data that you have.

DR. PIETRUSKO: Dr. Parenti can give you that.

CHAIRPERSON FERRIERI: Yes, thank you. This is on Ehrlichia.

DR. PARENTI: Just to take one step back to remind you of the numbers. In year one, we had 12 versus 15 cases for flu-like illness. In year two, there were 9 versus 18. Just to show you the -- since this group had to have Western blot sero conversion, I just want to review these numbers with you as well. In year one, again you can see the predominance of IgM sero conversion. And in year two again, most of the cases are predominantly IgM. We were also interested in these particular results, and initially we noted obviously that there was lower efficacy for this category than definite Lyme disease, and we noted this predominance of IgM. After the study was done, we also were made aware of the

results of blood PCRs that had been sent out to the Mayo clinic and became aware that we had 7 positive blood PCRs. At about the same time, we became aware of published reports in the literature suggesting that Ehrlichia may induce a false positive IgM.

So what we did was we took the baseline acute and convalescent sera on all subjects who had been evaluated for suspect flu-like illness, not just those that were cases. And we went back and looked at all the subjects who were considered definite Lyme disease based on their IgM's alone -- that that is the only way they got into the definite category. We sent that sera in blinded fashion to Dr. Persing out at Mayo Clinic and asked him to assay for Ehrlichia, Babesia, and also for Lyme disease. Dr. Persing has an IFA assay that he uses for diagnosing Lyme disease after an immuno-absorbent. He claimed that he could get around this particular issue, so we asked him to pursue that. These are the results. First, the people who were considered definite Lyme disease had no evidence of Ehrlichia. So we felt comfortable that the definite cases were still definite cases. When we looked at the flu-like illness, there were 8 people who had positive HGE titers -- I am sorry, 8 positive sero conversions for

Ehrlichia. They had new onset of Ehrlichia titers, either at their acute or convalescent sera. Two of those were in the first year. And as you can see, they were both in the placebo group. Interestingly, both of them still had positive IgM's for Lyme disease. So we concluded that these people were co-infected. They had Ehrlichia and they had Lyme disease. And there were no vaccinees who had Ehrlichia in the first year.

In the second year, there were six subjects who had positive titers for Ehrlichia -- two in the placebo group and four in the vaccine group. Now of the two that were in the placebo group, one of them still had a positive test for Lyme disease. So one of them looked like they were co-infected. The other person looks as if they have a false positive induced by Ehrlichia. When we get down to the vaccinees, there were four vaccinees, none of whom had a positive IgM for Lyme disease. Now we would propose that those are false positive Lyme Western blots induced by Ehrlichia. If you subtract these four cases and this one case here from the original numbers that I had shown you for the number of cases in year two, then the vaccine efficacy for flu-like illness in the second year is approximately 70 percent.

CHAIRPERSON FERRIERI: Regarding this data, I think there is someone who had a question. Dr. Snider?

DR. SNIDER: Well, it seems to get a little more confusing to me as we go along. But related to this case definition, I guess what I am hearing is that the possibles may not be actually Lyme disease. But if I look from year one to year two at the placebo group, I see that the number of definite cases went up from 40 to 61, which could mean there was more exposure in the placebo group the second year. If I look at the possibles, that is 24 and 24, which kind of goes along with a non-specific diagnosis. But then I am somewhat confounded by the fact that asymptomatic sero conversion remained the same from year one to year two -- basically the same, 12 and 13. And somehow I would have expected more asymptomatic sero conversions. In fact, approximately 50 percent more. And I don't know how to interpret this unless there is also something about the serologies that is strange. But the specificity seems to be borne out by the decrease in number of asymptomatic sero conversions in the vaccine group. Does anybody have any -- does the sponsor have any explanation for this phenomena?

DR. PARENTI: There are a couple of thoughts

there. Number one, the CDC data suggested that in 1996, I guess the second year of this study, the rates of Lyme disease were definitely increased compared to 1995. So when we saw the increased number of cases from year one to year two, it was pretty much in line with the CDC. I agree with you that the year two data don't go along with that. And again, what it is exactly that we are capturing in those possible Lyme disease and what some of these IgM only flu-like illnesses are, again we are not 100 percent sure.

As far as the asymptomatic sero conversions are concerned, there were a couple of additional asymptomatic sero conversions in the placebo group. So I believe if you look at the intention to treat analysis, the number of cases of asymptomatic sero conversions does go up in the placebo group.

CHAIRPERSON FERRIERI: While you are gathering that data, I wonder if one of you might respond to criticism that some people levy at the commercial Western blot kits and pre-immobilized blots. You used a standardized protocol so that all sera, I gather, were run in the same laboratory using the same technique with the same -- was it a commercial product that you were using?

DR. STEERE: Yes. The Western blot kit that

was used was manufactured by Mardex. And all tests were run in the same laboratory. I would also say again that sero conversion was required to document sero positivity, a negative and then a positive. And those tests had to be run together or at the same time.

CHAIRPERSON FERRIERI: Thank you. That is a very important point. Back to Dr. Parenti?

DR. PARENTI: Yes. The numbers are not as -- the numbers in the placebo group in year one, we had 15 asymptomatic sero converters. The number goes up to 17. So there were two additional -- no, I am sorry. They go from -- this is year one. So this is -- so there is a slight increase in asymptomatic sero conversion as well.

CHAIRPERSON FERRIERI: Dr. Kohl had a question, if we could pursue that.

DR. KOHL: Well, it is sort of a follow-up of Dr. Kaizon's question and Dr. Dattwyler's question. We have been, I think, dancing around the point a little bit. We have been shown data that the patients or the volunteers who got Lyme disease after being vaccinated, at least on a general curve, had a lower serological response after the second dose. We have also been shown data that there are some outliers who

have a disparity between the different types of antibody that you have tested. And I guess the basic question I would like you to answer is is there a protective level of either of these antibodies that we can hang a hat on, and then will that help us predict how often we will need to boost these individuals?

DR. PIETRUSKO: I would like to have Dr. Frank Rockhold come up to the speaker and answer that.

DR. ROCKHOLD: Frank Rockhold, SmithKline. That is something we are working on at the moment. We have certainly been able to show that the month two titer levels are predictive of efficacy. We are evaluating by a number of models. We are just trying to establish the level that you are seeking. Those data are currently under review by the FDA.

CHAIRPERSON FERRIERI: Thank you. It wasn't the plan today to review such data which apparently are still under discussion. So we won't have that benefit. Dr. Daum?

DR. DAUM: Thank you. My question is a variant on some of the other issues that have been touched on, but I would like to make sure that I understand it correctly. It has actually got three sort of interwoven parts. The first

one is as I understand everything that is being said so far, it is the belief of the company that it is antibody to OspA that protects you. And that the CMI may play some role perhaps in pathogenesis of an unwanted outcome of infection, but it is antibody that protects you. So if you don't have antibody, you are not protected. If you have antibody of some undefined certain level, you are. So question one is I would like that just clarified for sure.

Then question two relates to how this antibody works to protect you. I am just having a little trouble sorting things out in my mind. The tick bites you. It has got organisms in the mid gut that are expressing OspA. It has got organisms in the salivary gland that presumably are not, from what we have heard this morning. So it is this antibody which then leaves the human and goes to the tick and then pretty quickly, I would imagine, kills all the organisms in the mid gut. It probably doesn't do anything to the organisms in the salivary gland. And it therefore protects you against Lyme disease. I would like a comment as to whether that is a correct view of what you think happens.

And then the final question is I am struck by the fact that the antibody curves, which are logarithmic in

the y axis, actually are quite steep in terms of their runoff. So if it is correct that no antibody no protection, then while it was touted that at 24 months you end up with antibody similar to that which you ended up post-dose two, it is also true that 12 months earlier you had four or five times that amount of antibody, at least as judged by the geometric means, which admittedly don't give a feeling of the spread of the data. So it doesn't take long before you figure out that if all of these things I have said are correct -- and again I would like comment -- that you are going to need a lot of boosters here. Because it doesn't look like a lot of boosting is going on in nature as best you can judge by these geometric means without the feeling for the spread of the data. So I will stop there, but I would really like to hear comment on those three things.

DR. PIETRUSKO: Okay. I think the first question was concerning about the antibody, and I will have Dr. Lobet talk about that and the mechanism of action. And for your third point, I can address that part after that in the sequence.

DR. DAUM: Thank you.

DR. LOBET: Could you prepare the last slides

of my presentation, please? Now to answer your first question, indeed we expect that the antibodies will do the job. We do not expect CMI to do it -- I mean the transferral cells, somehow, to do the job. It has been shown in preclinical studies very early on that if you transfer antibodies, you can protect mice against change, while if you transfer cells, you will not.

Now regarding your second question on the mechanism of the protection by itself. At the time the tick feeds on the mammal, Borrelia burgdorferi is present in the mid gut. It is not present in the salivary glands. When it begins to feed there, it receives -- if you have no anti-OspA antibodies, it receives a signal from the blood. We don't know the origin or what is the nature of this signal. In this signal, we induce two things. The first is OspA will not be expressed any more by Borrelia burgdorferi. And the second thing is Borrelia burgdorferi will migrate from the mid gut to the salivary gland. So when you have anti-OspA antibodies, somehow it is too late for Borrelia burgdorferi to escape to the salivary glands because they have already been in contact with the anti-OspA antibodies. Does that answer your question?

DR. DAUM: Yes, it seems awfully quick. It has a little bit of a mushy feeling to it in that if they turn their anti-OspA off as quickly as you imply, then the antibody must also be acting more quickly than the bugs can. It is an awfully fast mechanism.

DR. LOBET: When I say -- well, I agree with you for the expression of OspA. That doesn't mean that OspA is removed from the surface of the bacteria.

DR. DAUM: I see. Okay.

CHAIRPERSON FERRIERI: As part of Dr. Daum's question, and please don't laugh -- have you done fine dissections then of the tick so that we know that the anatomy that you have exposed here is correct and that there is nothing then in the salivary glands?

DR. LOBET: Could you repeat that?

CHAIRPERSON FERRIERI: Yes. Have you dissected a tick so you know that there are no bugs in the salivary glands?

DR. LOBET: We have not done this, but some groups have done this. And to show not only that Borrelia burgdorferi is present in the mid gut and not in the salivary glands but also to show that OspA is indeed expressed in the

mid gut and not in the salivary glands.

CHAIRPERSON FERRIERI: Yes, please, Dr. Karzon.

DR. KARZON: Well, I am prompted at this point to bring up the question of neutralizing antibody. Amongst virologists, anyway, that is our golden path. This tick experiment is the closest thing to a neutralizing test that I have heard about today. But one could design a neutralizing antibody because you have a very nice mouse model I gather, and you could give passive antibody to the mouse that protect the mouse.

DR. LOBET: Yes, absolutely.

DR. KARZON: Okay. And with that model, it seems to me, you could do a titration of neutralizing antibody and compare that to the two binding titers that you now measure in-vitro to see whether they parallel. Even if they did, you wouldn't be certain of carrying over the biological function when you measure something by a simple attachment test in the serum. Our concern about the nature of the antibody and its protective level with certainty I think is real. Now it is not anybody's fault. This is the state of the art is what I am saying. But I wonder if we can go from here with the data we have. We have lots of sera. And do

enough work of a neutralization type to clear up some issues such as crossing with other antigens, which would cause confusion.

DR. LOBET: Could you repeat the end of your question?

DR. KARZON: The point I was just trying to make is that Ehrlichia antibody, for example, as measured in the test now, would this also be discerned in the neutralization test or can they be distinguished?

DR. LOBET: Against Borrelia burgdorferi?

DR. KARZON: I am looking for functional behavior of the antibody.

DR. LOBET: Okay. The LA-2 antibody, as was mentioned already several times here, is what you call a functional antibody because we know it is a bactericidal antibody, and also we know that if we transfer it to mice, we can protect those mice against subsequent challenge. So it shows that at least in most cases you have a good correlation between total IgG, anti-OspA, and the LA-2 titer, indicating that you have a good -- in most of the people, we have a good relationship between the two, total IgG and functional antibody. That is one thing. Now on the other side, the LA-2

antibody is only probably one of the epitopes that could be useful. You cannot exclude that other epitopes could be useful as well either to kill or to block the transmission. So I would see the LA-2 measurement as a minimal measurement of the quality of the antibody and not as a perfect measurement of the quality. So even if you have a low LA-2 antibody, you can exclude that you have other epitopes that are recognized by other antibodies that may work as well.

Now on defining the levels of antibody that is required, as has been mentioned earlier, this is under discussion right now with the FDA.

CHAIRPERSON FERRIERI: We still need to address Dr. Daum's third question, then. Bob, would you like to repeat it? The one on the antibody curves, the log scales, and possible need for multiple boosts.

DR. PIETRUSKO: Yes. And I think your point is well taken. We are currently pursuing that. We are looking at the information we have from 008. We are looking to define the correlative protection by various models, and we are looking also at differing dosing regimens to further answer that question. I think it is very appropriate. We don't have the answers now, but we are certainly looking at those.

DR. DAUM: But what is it exactly that you are pursuing. Because the data that runs off are pretty clear from the data you presented. So the question is only how often to maintain it. Or are there other issues that I didn't understand?

DR. PIETRUSKO: We are currently responding to various questions and we are working closely with the agency to actually come to a final determination of that particular information. We are looking at that.

CHAIRPERSON FERRIERI: Dr. Greenberg?

DR. GREENBERG: One of the theoretical questions was whether this vaccination could alter the course of wild type disease, and you said it didn't change the duration of EM. Did you look at your photographs and see whether it actually changed the look of EM? I assume since that is the diagnostic criteria most of the time, did it make more bull's eyes or less bull's eyes or however clinicians usually diagnosis this? Did it change the phenotype of the skin lesion?

DR. PIETRUSKO: Dr. Parenti will answer the question.

DR. PARENTI: After the study was done and

unblinded, I gave a series of photos to several investigators to see if they could tell vaccinees versus placebo, and they could not. We also went through a list with a couple of investigators of what they thought were some of the more atypical EMs. And Dr. Sikand had showed you a couple of those today. Again, the number of "atypical" ones that some of the investigators thought that weren't typical bull's eye were pretty much split between the two groups. So just looking at the photos, no, you couldn't tell the difference between the two.

CHAIRPERSON FERRIERI: Dr. Snider?

DR. SNIDER: I just want to make sure I understand correctly. I believe some studies were done in mice using human anti-outer surface protein A antibody for passive immunity. I was wondering if there have been no studies looking at what amount or what titer of antibody is required to sterilize the tick.

DR. PIETRUSKO: Dr. Lobet will present that information.

CHAIRPERSON FERRIERI: Good question.

DR. LOBET: Those experiments have been conducted indeed, and even with sera coming from Lyme 008. I

don't remember the titer by itself. It is clear that you can kill Borrelia burgdorferi and clear the Borrelia burgdorferi from the ticks. That is something that has been done in a very small number of animals because of technical difficulties. And that is the reason why I don't remember the titer on this. Now it is difficult to define the real titer on that basis because we don't know what is the behavior of the human serum in the mouse. So even if you had -- I mean, if I remembered the specific titer, I am not sure this would be -- it would be only vaguely indicative of what could happen in the human itself.

DR. SNIDER: But do you have or remember a ballpark figure? I think it would be interesting information to have. If we knew what amount or what titer in mice would sterilize ticks.

DR. LOBET: Frankly, no. If you want a range, I would say between .5 and 3. I cannot be --

CHAIRPERSON FERRIERI: Could you please repeat those numbers then?

DR. LOBET: Between .5 and 3 micrograms.

CHAIRPERSON FERRIERI: Between .5 and 3 micrograms.

DR. LOBET: But it must be verified.

DR. PIETRUSKO: Dr. Parenti, did you have some other information? It has been confirmed.

CHAIRPERSON FERRIERI: Do you have something else that you were going to add to that? Otherwise, I will move. I haven't forgotten those of you who have had your hand up. But Tom Fleming, could you repeat the question that led Dr. Pietrusko to pull out some other data, if you can remember it? Or Dr. Pietrusko, you know what the data is. Go ahead, Tom.

DR. FLEMING: I think, Patricia, was it the issue relating to the arthritis/arthralgias and tendinitis? We had 107 in year one and then 304 in years one and two presented to the data safety monitoring board where the board had indicated that there was --

DR. PIETRUSKO: That is the question. We have that information for you now.

DR. FLEMING: Okay. I have a related question to that, but do you want to go first with the answer?

DR. PIETRUSKO: Sure. We will show the information first. The question was whether it was balanced by placebo versus any groups.

DR. PARENTI: Dr. Steere had evaluated these subjects, and he had categorized this 107 subjects into the following category. Patients who had arthritis or tendinitis was one category. Patients in whom no physical exam was done. Patients with an alternative diagnosis for their joint symptom. And patients who had alternative diagnoses of osteoarthritis, overuse, fibromyalgia, et cetera. And I should point out here that there were 107 subjects in this analysis and this adds up to 102. There were three subjects for whom Dr. Halsey was not able to get the A/B envelope in time, and there were two subjects who were in this category but had been diagnosed as being a case of Lyme disease. So Dr. Halsey did not unblind those two. So that explains the 102 versus 107. As you can see, in each of these categories they are virtually evenly split between the two groups.

CHAIRPERSON FERRIERI: Please, Tom, go ahead.

DR. FLEMING: Just in terms of interpreting these data, which is the categorization of people with joint symptoms within one month, is it fair to interpret that these are predominantly what I might refer to as sub-elements of early disseminated infection as opposed to specifically treatment related late Lyme arthritis? Or another way of

stating this is do these data provide us any way of addressing whether or not an unintended adverse effect of a vaccine in influencing OspA and HLFA might have an adverse effect on pathogenesis of treatment resistant late Lyme arthritis? And again related to this is a 20-month study really adequate to assess whether we have an unintended adverse effect on late disease, chronic arthritis or neurologic abnormalities?

DR. PARENTI: Well, this indicates that again these were very early in the course. This is after two doses. So, again, prospectively we were looking at this issue. We knew it was an issue. Obviously, this doesn't totally address the question. But we have looked at it after two doses and we have looked at it at the end of the study. We have looked at it with this additional CMI data that has been generated. We have looked at it with 24-month data. And again, I think both the sponsor and the DSMB have concluded that we have no data to suggest that we are inducing a syndrome analogous to late resistant Lyme disease.

DR. FLEMING: But essentially we do have data and my interpretation is that these data are showing no association relative to sub-elements of what would be early disseminated infection, i.e., we can't glean from these data a

conclusion that in fact there isn't a potentially unintended adverse effect on this late treatment resistant Lyme arthritis.

DR. PARENTI: I am sorry, you keep saying this sub-element of.

DR. FLEMING: Well, when we talk about early disseminated infection, we are actually in that talking about elements that go beyond joint symptoms. We are talking about skin, heart, liver, et cetera. And what I am saying is these data are one element of early disseminated infection. So I see an answer here that is reassuring, and that answer is that there is not a vaccine-induced adverse effect on joint symptoms within a month. My question is -- my understanding is a much more global and a much more serious concern which relates to whether or not there could be an adverse effect on pathogenesis by affecting OspA and LFA's that would influence treatment resistant late Lyme arthritis, and I a just trying to get at the point that these data really don't address that concern. Is that a fair conclusion?

DR. PARENTI: The data that I just showed?

DR. FLEMING: Right.

DR. PARENTI: No. They are very early data.

DR. FLEMING: Right.

DR. PARENTI: But we have also showed late data to support the contention that, again, there is no relationship.

DR. FLEMING: And could you remind us of those late data that do show that?

DR. PARENTI: Sure. Number one, the DSMB reviewed the late onset adverse events. They reviewed the early onset adverse events after the study was unblinded, and what it showed was that there was a statistically higher rate of arthralgias in the vaccinees. Now when you looked at that, those were the same arthralgias that were occurring in the first couple days after vaccination. So after that period of time -- so that is accounted for. So if you look at the late onset arthritis, arthralgia, musculoskeletal in general, there is no difference between the vaccinees and the placebo subjects.

DR. FLEMING: But I don't recall seeing those such events recorded in the placebo either, i.e., my sense was that this study with its duration of follow-up was effectively giving us short-term answers, but these answers relating to these late events are really too early to be answered with

this data set.

DR. PARENTI: I am sorry, I am missing your point, Tom. I have got 20-month data comparing two groups.

CHAIRPERSON FERRIERI: Dr. Greenberg?

DR. GREENBERG: I am confused by the questions, Tom. I think -- so I may be not understanding your question either. I think you are confusing vaccine-associated effects and infection-associated effects, or at least what I am hearing -- could you try to clarify this because I am not following what is going on.

DR. FLEMING: I am glad you bring that up because both are important and I am trying to get at both. I am glad you mentioned that. There are, as I would understand it, both infection-related as well as unintended vaccine-induced risks of what we are referring to as treatment-resistant late Lyme arthritis or more generally the late Lyme disease consequences of chronic arthritis and neurologic abnormalities. And in terms of the infection-related, is it too early to tell whether the beneficial effects of the vaccine in reducing EM are also a clue for our hoped intention of reducing subsequent infection-related occurrence of these events. And in terms of the unintended vaccine effects, is it

possible that we may in fact be inducing a risk of such arthritis events unintentionally with the vaccine. And all I am trying to get at here with this clarification is it is my understanding that this study is really not able to address those late-term effects. It would take a longer term follow-up.

CHAIRPERSON FERRIERI: Well, let's let the sponsor respond first.

DR. PARENTI: David?

DR. KRAUSSE: David Krausse, SmithKline Beecham. I would just remind you, Dr. Fleming, that it was this committee that suggested that a 24-month follow-up was appropriate for the safety evaluation of a Lyme disease vaccine. Now the study -- the present study lasted 20 months, and the only reason that it stopped at 20 months was because we needed to -- we had promised the placebo recipients that we would cross them over in the third year if the vaccine were found to be safe and effective. So after 20 months, the study was unblinded and we continued to follow all the vaccine and placebo recipients for an additional four months in open label fashion, and those data were provided to the FDA and a very brief description of those data in your briefing document were

also provided. So I just wanted to point out that it was the committee that suggested 24 months for the duration of the follow-up.

I think that at least within the power of this study, it is fair to say that we could not discern any difference in the safety and any increased risk in the vaccines compared to the placebo recipients.

DR. FLEMING: And that we agree within the power of the study. I was getting more at what the study would not be powered to be able to address.

CHAIRPERSON FERRIERI: We have several other questions. If any of you have a precise question relating to this issue, keep your hand up. Otherwise, we are moving on to Dr. Poland. Steve, can your question hold or is it related to this very issue?

DR. KOHL: You will have to tell me. I want to get at this syndrome that Dr. Steere raised, which I think is related to this issue. Dr. Steere mentioned one patient who had an arthritis paresthesia syndrome. And in reading the safety data, there are actually two patients who are identified, patient 12340 and 10857, both of whom had a similar syndrome with arthritis and paresthesias and both of

whom were DR4 positive. Assuming that roughly 10 percent of the population that they vaccinated were DR4 positive, which is what the data suggests, that is 2 out of 500, whereas none of the ones who were DR4 negative seemed to have developed this syndrome. I wonder if the manufacturers want to address that as part of the safety issues.

CHAIRPERSON FERRIERI: Dr. Parenti?

DR. PARENTI: Let me just very briefly summarize the adverse events. There were, in fact, three subjects who had paresthesias and arthralgias. Two are in the vaccine group and one was in the placebo group. Now we don't know the HLA status of the placebo person because that work is still ongoing. Now of the two vaccinees, one subject did have paresthesias and arthralgias after dose two for several months. Those symptoms resolved, and when they returned at the end of the first year for the third dose, the symptoms had resolved and the investigator felt comfortable and gave them dose three and they did not have any return of those symptoms. And this is the subject that Dr. Lucey had discussed a year and three months later was found to have unexplained renal failure. So I don't know how to put that story together with having a vaccinated subjected developing paresthesias and

arthralgias when we have two on vaccine and one on placebo and one of the vaccinees gets it after two doses but doesn't get it after a third dose. I am not really sure how to put that in any specific theory.

CHAIRPERSON FERRIERI: Dr. Broome?

DR. PARENTI: But those are the three subjects that Dr. Steere mentioned and on whom we have data.

CHAIRPERSON FERRIERI: Dr. Broome?

DR. BROOME: Just to try to understand what the study exclusion criteria might mean for this. Do you have any sense of whether the frequency of the HLA DRB1 0401 and other rheumatoid arthritis alleles is similar in the study population to the general population?

DR. PARENTI: Allen, could you comment on that?

DR. STEERE: I don't really know. And one of the reasons is that the ability to do this kind of subtyping that involves sequencing is new, and the sort of epidemiologic study that you would like I don't think has really been done.

CHAIRPERSON FERRIERI: Dr. Poland?

DR. POLAND: Claire, I can say that the frequency of the DR4 alleles that has been quoted of 10 percent is in the Caucasian U.S. population. I don't know

what it would be in other populations. Along those lines, I had several questions. The subject 10857, did she happen to get the vaccine into her left arm?

DR. PIETRUSKO: Dr. Parenti?

DR. PARENTI: Yes.

DR. POLAND: Then I will tell you my theory later. Have the subjects in the Lyme 008 that had vaccine failure, have they been HLA typed?

DR. PARENTI: No.

DR. POLAND: Okay. The other question I have -- Tom may be able to offer some help here. In the discussion about the theoretical concern of the vaccine inducing any kind of rheumatologic problem in patients who are DR4 positive, what is the power of the study to determine those thresholds? If we said, well, the risk was 10 percent, for example, and we guessed that 10 percent of them carried the DR4 allele, what kind of power do we have to determine if the vaccine theoretically did induce any type of rheumatologic disorder? Do we know the answer to that question from your statisticians? In other words, clearly we are not seeing it at 202 months, but is that a type 2 error?

DR. PIETRUSKO: Dr. Krausse has some

information.

DR. KRAUSSE: I am not sure that we have the answer to your question, Dr. Poland. Just to say that from a clinical point of view, I am not sure that it is relevant. I think it is of interest from an academic point of view. Of course, there is no way that we could screen people for HLA haplotype prior to vaccinating them. Even in a study, just a subset were done. Of the 40 people who were HLA haplotyped of the 109 sequential vaccine recipients -- people who got vaccine and had sufficient cells for HLA haplotyping -- six of them had DR alleles in question. So that would be a frequency of 18 percent, which is approximately equal to the numbers that are thought to be -- I think you said 10 percent and some people say 20 percent. So that probably is representative of the whole population, which probably was somewhat homogeneous from a demographic point of view.

DR. POLAND: It is a concern I think more than academic when and if this vaccine were to be delivered to millions of people as opposed to a small number. And I think there would be a study that could be done to get at this as has been done with looking at vaccine failure with extended haplotypes for Hep B vaccine, and that is to prospectively

immunize subjects who are known DR4's. And those are actually not -- because of the relatively high frequency of that allele in the U.S. population and the frequency with which people get typed, perhaps they are bone marrow donors or whatever, you actually could prospectively immunize a large group of DR4's and perhaps get at that issue.

DR. KRAUSSE: I don't mean to imply that safety issues are of academic issues only. It is just practical issues versus theoretical issues. I think it would be very difficult to type people and then to vaccinate them. It seems to me that what is important is the frequency of adverse events in the entire population. So as I say, within the power of this study, we did not detect a difference. And if there was an increased frequency of adverse events of 1 in 1,000, I think that one would need a study of about 40,000 to detect a significant difference. If the difference were 1 in 5,000, it would probably take several hundred thousand vaccinees to detect that difference.

CHAIRPERSON FERRIERI: Dr. Patricia Coyle?

DR. COYLE: I think the possibility that vaccination might change the clinical picture of infection is of some concern. Really, the vaccine is not 100 percent

effect. It is not just of theoretic interest. There are two distinct animal models that suggest that when this single protein vaccine is used, some of the hosts do get infected but it is a smoldering infection that becomes more difficult to detect. Now vaccination is going to mess up serologic detection. I think in the monkey model, you had antigen and PCR and pathologic data of infection in some of the animals vaccinated. And in the rabbit model, you lost EM, which was a very good marker of infection. And this brings us back to the possible Lyme disease group, which is somewhat problematic. We heard that at least some of 2.2 perhaps may be explained by co-infection with HGE. You would like the same rigorous application to the asymptomatic sero positives to document that they are not co-infected as well. But it doesn't explain 2.1. Even with the laboratory data being negative, that doesn't exclude that they had a valid EM. So my question is for those possible Lyme disease patients, were they treated or were they not treated? And if they were not treated, have they been followed and have any further specific testing been done on that group?

DR. PIETRUSKO: Dr. Parenti, do we have some information on that topic as far as the latter part?

DR. PARENTI: I don't have any specific information about whether they were treated. My presumption is that they were, number one, told that they had sero conversion and that they were treated and the decision about treating clinical EMs was left up to the investigator. My presumption is that the vast majority, if not all of them, were treated. So, no, I don't think that we are going to have data on these "untreated" Lyme disease subjects.

CHAIRPERSON FERRIERI: Does that answer your question, Dr. Coyle?

DR. COYLE: Yes.

CHAIRPERSON FERRIERI: Dr. Greenberg, do you still -- you don't have anything? Dr. Finkelstein?

DR. FINKELSTEIN: I wanted to ask some questions about the design of the study. I found the case rate to be kind of low in this population. So I was wondering whether you thought this was really the optimal target population, and if not, what were the implications about the generalizability of the study to a target population? And the second question is to speak to the timing of the vaccine, whether you thought that was optimal. And if not, what is the generalizability again to changing this?

DR. PIETRUSKO: Okay. I will have Dr. Parenti talk about the clinical cases as well as the applicability of the ultimate design for the protective efficacy of the product.

DR. PARENTI: I am sorry, I missed the beginning of your first question. You were asking in regard to our initial assumption as to what attack rates were versus what they ended up?

DR. FINKELSTEIN: No. Actually, I was saying that the case rates were rather low. So I was wondering if this was really the optimal population, and if not, how generalizable is this study to what would be the optimal population?

DR. PARENTI: When we initially started this study in 1994, there was a lot of discussion about what should we base the sample size on, what is the attack rate in the population. And those numbers -- a lot of numbers were considered. Ultimately the sample size was justified based on a very conservative rate of 0.5 percent attack rate. So we thought that was very conservative. As Dr. Steere has mentioned, we went to the most intensely endemic areas that we could find. I believe the attack rate in the placebo group

for the first year was just under 2 percent and I think it was just over 2 percent for the second year. So that is pretty much -- obviously, that is a little bit more than we had actually thought that it would turn out to be. So, yes, I do think it is generalizable.

Your second question was in regard to the optimal schedule.

DR. FINKELSTEIN: Right.

DR. PARENTI: Obviously we did this study on a 0, 1, 12. We administered the dose just before the onset of the tick season. That seemed to just intuitively make the most sense. We would currently suggest that that be done as well. If it is licensed, that people get the second or third dose just prior to the onset of the tick season. Having said that, we also realize that 0, 1, 12 is perhaps not the most flexible or user-friendly schedule in the world and that alternative schedules -- we are pursuing alternative schedules to obviate that need and to give subjects and practitioners a little bit more flexibility in administering doses for people who we have forgotten or not been in the area but wanted to be vaccinated for the ensuing season. We plan to have alternative schedules, and I mentioned them earlier, available

so that if the GMTs after three doses in alternative schedules equal the GMTs after the third dose of Lyme 008 then we think that would be possible.

CHAIRPERSON FERRIERI: Dr. Kohl?

DR. KOHL: This is a theoretical question. It may sound like it is coming from outer space, but I will try to explain it. It is for Dr. Steere. LFA-1 is really a fascinating protein. It is an adhesive protein that allows lymphocytes to stick and kill other cells when they have to or communicate with other cells. And in children who lack LFA-1, there are severe immunodeficiency syndromes associated with that. I wonder if it is at all possible that some of the antibody that is cross-reacting to LFA-1 may down-regulate T cells or have negative effects on T cells. Has that been studied in-vitro possibly or in-vivo in any way?

DR. STEERE: We don't think that the antibody binds to LFA-1. It is a dominant T cell epitope of OspA that has molecular mimicry with LFA. How it all works is another story. We don't know that.

DR. KOHL: So there is a cellular but not a humoral cross-reactivity?

DR. STEERE: That is right.

DR. ELKINS: Excuse me, if we could be clearer, Dr. Steere?

DR. STEERE: Pardon?

DR. ELKINS: It is our understanding that there is no direct data that addresses the question of anti-OspA antibodies binding to LFA-1, is that correct?

DR. STEERE: Well, that is true.

CHAIRPERSON FERRIERI: Other questions from the panel here? Yes, Dr. Eickhoff?

DR. EICKHOFF: This is a follow-up question, I believe probably for Dr. Steere, about category 2.1 again. Remember, this is physician-diagnosed EM without laboratory confirmation. And Dr. Steere, I think you alleged that somehow these may have represented atypical cutaneous lesions that were mistakenly diagnosed as Lyme, is that correct?

DR. STEERE: That would be my first choice in that all the laboratory data was negative. I mean the other interpretation is that they did have Borrelia burgdorferi infection but that we were not able to document it by laboratory test.

DR. EICKHOFF: I guess my question is recognizing that in category 1 the lesions were photographed,

were any or all of these lesions photographed?

DR. STEERE: Oh, yes, they were.

DR. EICKHOFF: Is there any way of supporting or lending some credence to the notion that these were a group of atypical lesions?

DR. STEERE: On the way they looked, I would say the answer to that -- I mean, there can be classic erythema migrans. But I personally found it a difficult exercise deciding whether a lesion was erythema migrans or not based on a picture. I personally had a lot of trouble doing it.

CHAIRPERSON FERRIERI: Thank you. Dr. Hall?

DR. HALL: May I just ask if you can eradicate the antibody response by early treatment? In other words, somebody who say has EM or thought to have Borrelia burgdorferi infection, give them antibiotics immediately. Will you eradicate the antibody response?

DR. STEERE: You may eradicate the antibody response entirely by early treatment. But more commonly, you will see an antibody response in convalescence than you see acutely. So in other words even people that you treat now, if you come back four weeks later and do an antibody titer, you

are more likely to be able to show sero positivity then than you were acutely. So in this study we were getting up into the 70 percent range in convalescence that we could show sero conversion in the definite group.

CHAIRPERSON FERRIERI: Dr. Steere, could you refresh my memory on the PCR assay and when it was done on some of the patients, it was all done by the same technique I imagine. What were we amplifying? I have forgotten.

DR. STEERE: Yes, it was done by the same technique. The most experience is targeting ironically the gene for outer surface protein A. So that is what we were doing. We were using a primer probe set that targeted the plasmid gene for outer surface protein A.

CHAIRPERSON FERRIERI: Thank you. Dr. Poland?

DR. POLAND: Two questions. The first is you mentioned that the cut-off for sero positivity was 30 EIA units, and I was wondering how that threshold got established.

DR. PIETRUSKO: Dr. Dani DeGrave.

DR. DeGRAVE: SmithKline Beecham. This has been established in different ways. The first way was to screen with the final assay protocol. To screen subjects who had been entered in the studies, have been tested before for

Borrelia burgdorferi antibodies. And titers have been titrated for these samples and the rates have been established and this was found to be around 10 ELISA units per ml. So that is the 20 ELISA units that we used as a cutoff. Another way was to look for the specificity of the samples and to absorb out -- I am sorry, this is another point. So basically we had over 300 samples that were included in different studies. They have been assayed by the final assay protocol and were found to be below this 20 ELISA units per ml cutoff.

DR. POLAND: The other question I have is that not surprisingly in any study of this magnitude, and in fact the dropouts seem lower than normal in this. And I may have missed it, but was there any difference between the vaccine and placebo group in the rate of drop-out. And then within the drop-outs, anything that showed up as differences between the two groups?

DR. PIETRUSKO: Dr. Parenti has that information.

DR. POLAND: I think there were somewhere in excess of 500 dropouts.

DR. PIETRUSKO: We will have the information as soon as he finds the overhead.

CHAIRPERSON FERRIERI: While he is looking for it, I would remind the committee members that we will try to wrap up, if we can. I think our questions are decreasing in number. We will try to wrap this up and then get back to FDA's presentation of the questions. And then we can have further committee discussion. But try to exhaust your questions for information now from the sponsor.

DR. PARENTI: Can I have slide #41 of Dr. Steere's carousel?

DR. KARZON: I believe Dr. Broome brought up briefly another topic that we really haven't discussed a whole lot, and that is how this vaccine will be used. And under this heading, I would be interested to know what your group would write down as the exclusions. Who should not receive the vaccine? We have had some new experiences since this question was raised initially. I would like to know whether there will be cardiac exclusions and how this would be screened, and in particular how we will handle individuals with arthritis of all kinds of etiologies, especially if we get into older age groups, and any other exclusions. And then how we will handle the question of who should receive the vaccines. I know you listed initially the logical conditions

of putting people who are at risk. It would be interesting -- this probably would embrace a great many people, a high percentage of the population in certain parts of the country. And even on the question of how it should be used in more sporadic regions. This may be a lot of people, as I am sure you have probably calculated. Therefore, we must pay particular attention to low incidence adverse effects, not just an incidence in the 1 percent or above, but things that happen less than that. And this will inevitably appear in this disease in particular. In poliomyelitis, to give an old analogy, we are still struggling with the extraordinarily low rate of adverse events as a serious issue. And here it is more complex because I think defining things will not be as easy as it is in polio in the patient or contact. These loom to me as very major problems that we will have to think a lot about, and I am sure you have been thinking a great deal about these sorts of issues.

CHAIRPERSON FERRIERI: Let us proceed with this data and then we will have room for more questions.

DR. PARENTI: So on this slide we have the number of subjects who start and the number of subjects who completed the study. So you can see that statistically there

is no difference between the number who completed between the two groups. The number of subjects who discontinued because of serious adverse events again were similar in both groups, 16 versus 11. When you look at the ones that were related or possibly related to the vaccination, 2 versus 1. And again, of other adverse events that are related or possibly related, 9 in the vaccine group versus 2 in the placebo group.

This is a table just going into the specific events that led to study termination. The most common was early onset of arthralgias. Otherwise, I think the rest of the events are fairly common -- arthralgias and perhaps paresthesias. Otherwise, the events are very similar.

CHAIRPERSON FERRIERI: Any question on this data? The issues that Dr. Karzon brings up are very fundamental to what the committee can contribute to FDA and maybe we could hold on those. I would like the committee to wrap on some of those issues and I would like to get to these other specific questions. So we will start with Dr. Luft and then Patricia Coyle and then Dattwyler.

DR. LUFT: I just want to make one comment on that last point. I think it is important for us to understand what the adverse events would be vis-a-vis the serious

sequelae or the incidence of the serious sequelae due to this disease and what is the trend in regard to the serious sequelae. It didn't escape any of us, the last comment that was made before the break that with good vigilance that the number of cases that were actually diagnosed was really quite high for Lyme disease.

The point that I wanted to make in regard to the study is that there is very heavy dependence on serologic confirmation. And when we start thinking about the adverse events, it was stated originally when we got the overview of the disease that the disease is really quite protean. And actually the adverse events are very similar to what the disease manifestations are. And if you start to, as I think Dr. Hall was eluding to -- if you start to kind of say well how often do you actually become sero positive, you can start to have a different take on when someone has an adverse event of whether it is disease specific or infection specific versus vaccine specific. And I think that that is an important issue that we have to deal with. I can only say from my own experience, having done a randomized double-blind controlled study that was FDA approved regarding the comparison of ezithromycin to amoxicillin, when we found that ezithromycin

was not as effective as amoxicillin, those patients when they had their disease related events were sero negative at the time that they had those events. So the serologic criteria would not have -- they would have done very well actually with these criteria, and I think Pfizer would have been much happier with me than they turned out to be.

So I just wanted to kind of ask in regard to that, and I think it goes back to an earlier question that I asked in regard to the self-reported events and whether there was any segregation that occurred between the 10 percent of patients reporting that they were having symptomatology, whether there was any difference between the vaccine group and the placebo group independent of antibody or serologic diagnosis.

DR. PIETRUSKO: Dr. Parenti?

DR. PARENTI: Basically the two groups had the same suspect symptoms. We didn't put it through statistical rigor, but when you looked at what it is that people came into the office with, what complaints, there was basically the same complaints in both groups. So both groups were being evaluated for the same things.

CHAIRPERSON FERRIERI: Dr. Dattwyler?

DR. DATTWYLER: I just wanted to ask in the category 1, what was the sero conversion rate in culture confirmed erythema migrans? Because then we might get a better handle on 2.1 that way.

DR. PIETRUSKO: Dr. Parenti will be looking that up right now.

DR. DATTWYLER: Okay.

DR. PIETRUSKO: Dr. Steere is going to answer the question.

DR. STEERE: Well, this slide shows the number that had sero conversion. But what you are wanting to know is the number -- okay. Well then that is very similar to what it was overall. In other words, to have any sero conversion, meaning both or either IgG or IgM, the sero conversation rate of 61.5 percent overall in the study population. It was 64 percent. So in other words, in the culture positive group, it was very similar.

DR. DATTWYLER: Okay. So if that is the case, say 64 percent or between 60 and 65 percent, that means that you might expect to see people in 2.1 who really have erythema migrans but could fall out into the you just didn't culture it and you didn't sero convert. Sero conversion is obviously not

universal. So that that 2.1 may contain real erythema migrans.

DR. STEERE: It may.

DR. DATTWYLER: And if you over-emphasize serology, you might miss that.

CHAIRPERSON FERRIERI: That is a terribly important point. There are several other individuals. We will go on next to Patricia Coyle and then Dr. Broome, Steve Kohl, and Fleming.

DR. COYLE: I just have three quick questions. In the proliferation interferon gamma assays, lipidated OspA was not used because the lipid acts as a mitogen. If you use lipidated OspA, what do the placebo and vaccine patients look like?

DR. STEERE: I don't know. I haven't done it.

DR. COYLE: It wasn't done. Okay. Secondly, knowing how this vaccine would have to be used if it was approved in endemic areas, is there any, any, any animal or human data on repetitive vaccinations -- multiple times?

DR. PIETRUSKO: Dr. Lobet, is there anything in animal repeat?

DR. LOBET: Your question relates to multiple -

DR. COYLE: Multiple vaccinations.

DR. LOBET: No, but there are -- there is no animal model that has been used for that, but we have some human data on this.

DR. COYLE: Some human data on like how many times?

CHAIRPERSON FERRIERI: How many boosters or challenges?

DR. PIETRUSKO: Dr. Parenti?

DR. PARENTI: We have one study where approximately 500 subjects have received 4 doses in a year -- 0, 1, 12, and 12. We have ongoing studies where people have received 0, 1, and 12 and have gotten a booster at month 24, and another cohort of about 150 or 200 who have gone 0, 1, 12, 24, and 36. And from the safety data we have right now, we are not aware of any unusual events happening in these people who have received four or five doses.

DR. COYLE: And my final question, this exclusion in the Phase III study of patients with joint problems was a little bit vague. So I am trying to get a feel of who was excluded. Would anybody in general complaining of

any history of joint pains have been excluded or current joint pains? Obviously rheumatoid arthritis and osteoarthritis, fine. But was it extrapolated, and just give me a sense of who was excluded based on joint problems.

DR. PARENTI: Yes, that is a good question. The gist that we tried to give the investigators was that we did not want people in this study in whom it would be difficult to assess for Lyme disease later. I mean one of the endpoints is looking for arthritis. So if you started out with arthritis -- we didn't want to make it -- we didn't want to have subjects who already had unexplained knee effusions, for example. So with those guidelines, we asked the investigators to use their judgment. So some investigators felt that back pain obviously wasn't an issue. They could clearly differentiate back pain from Lyme disease. There were investigators who had had some of these subjects in their private practice for years and years, they knew their osteoarthritis -- they knew their patterns of osteoarthritis and felt very comfortable that they could discern in a given patient whether there was a new event, for example. So we knew that this was an issue and we went back and looked at all the subjects who had musculoskeletal complaints at baseline to

see if, again, vaccinees who had a previous history of musculoskeletal complaints or had something on physical exam at the beginning of this study were at increased risk of developing subsequent musculoskeletal events. And from the table I have up here -- I apologize that the numbers are not really very clear -- you will see that as you go from dose 1 to 2 to 3 and look at musculoskeletal disorders, there is no difference between the two groups. So if you had a baseline history of a musculoskeletal event and got vaccinated, you did not appear to be at increased risk. And it looks as if there was over 2,000 such subjects. So 20 percent of the population already has some baseline musculoskeletal event, which is pretty much what you expect when you are looking at 40, 50, 60 et cetera year subjects.

DR. COYLE: Thank you.

CHAIRPERSON FERRIERI: Dr. Broome and then Dr. Kohl. Dr. Breiman, would you like to start?

DR. BREIMAN: Could I just --

CHAIRPERSON FERRIERI: Sure.

DR. BREIMAN: I may have missed the answer, but do you know what the actual number is of people that were excluded from the study because of joint problems?

DR. PIETRUSKO: Dr. Parenti? Do you want to give us that number?

DR. PARENTI: Do you mean people who were screened for the study and not entered because of that? No, I don't know.

CHAIRPERSON FERRIERI: Dr. Broome?

DR. BROOME: I am looking at the question we are going to have to address about the appropriate schedule for immunizing, and I would like to know the interval between the second dose of vaccine and the onset of disease for the failures. I really think that that is important information. As Dr. Lucey has suggested with his nice analysis, there is a very rapid fall off in antibody. And my hypothesis would be that when you look at the reverse cumulative distribution for the cases, there are some of them that had a poor response. So that is very credible. But those that apparently had a somewhat reasonable response, did they occur later in Lyme season? Does this help you confirm the concerns that there is a pretty rapid fall off of the antibody that may relate to protection?

DR. PIETRUSKO: Dr. Parenti is going to be answering the question. He is getting the information now.

CHAIRPERSON FERRIERI: All of this background information is quite critical to our addressing the questions. So if any of you seem dismayed, don't be. We will be getting to the questions fairly soon. Dr. Parenti?

DR. PARENTI: Slide 64 and 65 in Dr. Steere's. These are survival curves. I am sorry, this doesn't specifically have the titers on here. But as you can see, during year one the starting point here is from four weeks after the second dose to the onset of case. There is really no difference. The vaccine cases and the placebo cases are occurring within the same time frame. You will see the same pattern in the second year. Again, there are very few cases, but the vaccine cases are occurring in here.

I have a list. It is not a pretty list, but these are the vaccine failures from year two and their GMTs. It also has their onset dates. So, again, I had previously said there are 7 vaccinees who are -- there are 7 vaccinees who are over the age of 60 and six of them are over the age of 65. So if you just want to go through them very quickly, here is a 60-year-old who had virtually no response at all to the first two doses. They showed up in the middle of August as a year two case. I am sorry, I should step back a second. We

have blood on baseline on everybody and we have month two, but we don't have month 13 on everyone. The 67-year-old, again -- I'm sorry, this person actually had a fairly decent anti-OspA titer after the first two doses. At the end of the first year, they had lost it and they had the onset of their disease in mid-August. And at the time of the acute sera or at the time of the acute attack rather, you can see that they had GMTs in the 300 to 500 range. A 62-year-old with a minimal response to the first two doses. The onset of disease in year two at the very beginning -- I am sorry, onset of disease again in August. A 68-year-old, minimal response to the first two doses. Onset of disease in August. Unfortunately, they didn't have sera that were available to see what their titers were at that time. A 69-year-old, again poor response to the first two doses. They had their onset of disease in June, and again minimal anti-OspA response here. A 70-year-old, virtually no response through the whole thing. They had the onset of disease at the end of the season in September. A 68-year-old here, again virtually no response at all with onset in June.

CHAIRPERSON FERRIERI: Thank you. We will move on to Steve Kohl, please.

DR. KOHL: Yes. If you take category 2.2 and remove all the possible Ehrlichiosis cases and take category 3 and combine those two -- collapse those two into each other, assuming that the category 2.2's are really asymptomatic infection, what is the protection rate and what is the significance?

DR. PIETRUSKO: Dr. Parenti?

DR. PARENTI: Take 2.2 and what?

DR. KOHL: Take 2.2 and remove the Ehrlichiosis cases or the cases that you think are Ehrlichiosis cases and collapse that into category 3. What would the protection rate be if you combined those?

DR. PARENTI: I would have to do some quick math because we have not combined category 2.2 and 3 because one is possible --

DR. KOHL: The reason I asked that is you have combined just about every other category in the analysis except for that.

DR. PARENTI: We did it specifically at the FDA request. But to us, there are two separate things. One possible disease mainly based on IgM in fact in the 2.2 category, and category 3 clearly being no symptoms based on

IgG. But if you want, we can crunch those numbers for you.

DR. KOHL: Okay.

CHAIRPERSON FERRIERI: Thank you. Dr. Fleming?

DR. FLEMING: In preparing for the questions, I would like to just probe a bit. Thinking through what had been presented to us as the three stages of disease, I would be interested in a clarification of the clinical importance in timing, both from colleagues on the committee as well as from the sponsor. Very quickly, it has been presented to us that the three stages of the disease include the early localized infection and erythema migrans is a key aspect of that. In fact, 27 percent of the definite cases are EM cases. Then there is the early disseminated infection that includes spread to heart, liver, and joints. And then what we refer to as -- or what you refer to as late Lyme disease with chronic arthritis and neurologic abnormalities.

The first question is as we think of clinical importance, is it proper to -- or is it an appropriate clinical perspective that the clinical significance of the sequelae of infection is substantially enhanced by risks other than EM? Or if EM was the only clinical consequence -- another way of saying this -- the concern with Lyme disease

would be discernibly less? is that a fair conclusion?

DR. PIETRUSKO: Dr. Schoen is going to answer that question for us.

DR. SCHOEN: I think I will ask a question first and make sure I understand the question. I think that these categories of early and late, localized and disseminated, are rules of thumb that are helpful to the clinician. And as a rheumatologist, as I was listening earlier on to the discussion, I was struck by the fact that what I typically encounter in terms of Lyme arthritis in natural infection these days is patients -- if I had to make up a clinical story, it is a patient who has an erythema migrans rash in the summer which is missed or is perhaps not recognized. If it is not recognized, I can't say that it is in that particular summer. But it is certainly my impression as a clinician these days that a lot of the Lyme arthritis that I see, I am seeing in the fall or early winter following a transmission season. So I think that we would capture -- talking earlier about refractory Lyme arthritis and theoretical concerns about refractory Lyme arthritis, at least in natural infection refractory Lyme arthritis is an entity which typically occurs within months after the onset of

illness. It is obvious, as Allen mentioned earlier on -- Dr. Steere -- you see cases in which there are intermittent attacks of arthritis. You also see cases less commonly where almost from the start you have a sense that the arthritis is not going to go away. And if it persists for a long enough period of time, it is considered to be chronic.

So getting back to the question, which I wondered away from because I did want to make that comment, I think that it is helpful to think about early and late disease. And clearly something happens between early disease, which is easy to treat, and as Dr. Luft points out, if we didn't ever miss it, we wouldn't need a vaccine. But we do miss it. And late disease, where presumably some other pathogenesis is at work because it is hard to treat. But I would think of these as useful rules of thumb. And I don't think that the statistical information is invalidated. I think if we have eradicated the disease early, it doesn't have a chance to occur late and demonstrate a statistical difference.

DR. FLEMING: You are actually answering the second question, so let's just pursue that for a quick second. What you are saying then is if we wanted to be able to judge

our influence on chronic arthritis or the neurologic abnormalities that have been referred to as late Lyme disease, are you saying -- as a rule of thumb, roughly what time frame would you need to be able to assess those effects or those consequences from initial infection?

DR. SCHOEN: Well, I think it is a bell-shaped curve, which you can tell me more about than I can.

DR. FLEMING: Yes.

DR. SCHOEN: I would think that it is typically measured in -- and Allen may correct me here -- but I would say the average case occurs within a year. The average case I would say probably occurs within a year. And some cases occur much more quickly. I think I have seen someone who developed Lyme arthritis 11 years after erythema migrans, but that is the only case like that I have ever seen.

DR. FLEMING: So essentially it should be enough to follow a cohort for 20 months to be able to determine whether there will be a rate of chronic arthritis?

DR. SCHOEN: Yes. As investigators, we kept out of the study as much as possible anybody that we suspected had active infection at the onset of illness. So in an ideal world, nobody -- a few did, but nobody came into this study

with Lyme disease. We then had a surveillance in which we were very much helped by our volunteers to scour the land to find early disease and treat it. So we didn't see late disease, which I think we would have seen if it was going to break through.

DR. FLEMING: So in the placebo arm of this trial, we should be able to define how frequently then chronic arthritis occurred? Because you are saying we will know that answer within 20 months?

DR. SCHOEN: No, because --

DR. FLEMING: Refractory chronic arthritis.

DR. SCHOEN: The answer to how frequently it occurs depends on whether or not the disease is treated. If you treat the disease early, you don't see the late manifestations of disease. So if surveillance and capture of early cases was excellent, where are the late cases going to come in such a study?

DR. FLEMING: So essentially what you are saying is -- to modify my comment -- 20 months is enough for us to detect the frequency with which chronic arthritis will occur following infection, but in this study that rate may be very low in the placebo arm because of good surveillance and

effective antibiotic therapy?

DR. SCHOEN: I think that is true.

DR. FLEMING: And then the answer to the first question was if the only clinical consequence of Lyme disease was EM, the overall clinical sequelae would be much less serious than when we look more globally at other components including arthritis and other disseminated circumstances or consequences. Is that correct to say as a clinician?

DR. SCHOEN: As a clinician, if you are seeing -- EM is less serious than late manifestations. At least I think that is what you are asking.

DR. FLEMING: Yes. What I am saying is the fact that there are these late manifestations and other disseminated aspects to the disease that are sequelae to infection beyond EM are very important -- are certainly very important to the overall clinical consequences.

DR. SCHOEN: That is true.

CHAIRPERSON FERRIERI: Dr. Dattwyler?

DR. DATTWYLER: I agree with what Dr. Schoen has said. One point though is that chronic arthritis under any circumstances has become a rare event. The most comment -- the scenario of Lyme arthritis is what Dr. Steere's

described, arthralgias followed by usually knee effusion, spontaneous remission, and the sequence is repeated. And gradually the interval between episodes lengthens and the disease goes away. So real chronic arthritis is not the rule, it is the exception. And I think that that is an important point that everybody should realize. But otherwise, I agree with what was said.

CHAIRPERSON FERRIERI: Thank you. We have time for one quick question, and this will be Clement-Mann. And then we will have Dr. Elkins present the questions.

DR. CLEMENTS-MANN: I just wanted to ask a question. I was actually -- the K curve on this vaccine is not unlike hepatitis B, and I was wondering if -- you seem to get a good immunologic response with the third immunization. Evidence that looks suggestive of immunologic memory. But in the people who got vaccinated the third year, when they got the boost at 24 months and then they got the boost at the third year, did you see the same good response in terms of antibody rise or was it less or how did that look?

DR. PIETRUSKO: Dr. Parenti will discuss that.

DR. PARENTI: We are still evaluating that. The subjects who received the dose --

CHAIRPERSON FERRIERI: Would you speak into the microphone?

DR. PARENTI: The subjects who received the dose at month 24 and 36, we are going to be getting their serology this summer. So that is one of the issues we want to go back and look at. Does previous response predict future response, et cetera?

DR. CLEMENTS-MANN: And just quickly, was there any difference at all in terms of that responsiveness to the booster, even at 24 months, in individuals who had been previously infected?

DR. PARENTI: Again, from the preliminary look that we had, the previous infection issue did not really seem to play a part at all or a role at all. Could I make two very quick comments?

CHAIRPERSON FERRIERI: Very briefly.

DR. PARENTI: Okay. Number one, for Dr. Fleming, we did follow some of the vaccinees -- approximately one-third of the vaccine population was followed for an additional year to see if they developed Lyme disease, and they did not. So we have followed some of those. And the second thing is in regard to your question of if we combine.

At year one, there were no Ehrlichia, potential false positive Ehrlichia, so we don't change the numbers there. But in year two, we would have had five vaccinees versus 30 placebo for an attack rate of 83 percent if we combine the 2.2 and the category 3's.

CHAIRPERSON FERRIERI: Thank you. Dr. Elkins, there are two ways of looking at this. That we are an hour and 40 minutes behind or an hour and 40 minutes ahead. I am an optimist, so I feel we are an hour and 40 minutes ahead.

DR. ELKINS: You may wish to consider the afternoon break before we do questions.

CHAIRPERSON FERRIERI: No, I would prefer that we do the questions and then we will have a break and then we will come back and do the open public hearing. And then we will deal with more committee discussion and actual votes.

DR. ELKINS: All right, then. The questions which we wish to put to consideration for advisory committee members this afternoon include the following. First, are the data sufficient to support the conclusion that the vaccine is safe for immunization of individuals 15 to 70 years of age? And within that overall questions, we would particularly appreciate comment from advisory committee members on the

adequacy of the long-term follow-up data, on any cautions for those with chronic joint disease or others who were excluded in the pivotal efficacy trial, and on the use of Lyme disease vaccine in those persons with a previous history of Lyme disease.

Number two, are the data sufficient to support the conclusion that the vaccine is effective against definite Lyme disease in individuals 15 to 70 years of age when given on a 0, 1, 12-month schedule? And we are particularly interested in advisory members' comment on the appropriate description of the overall efficacy results and the demonstration of protection against asymptomatic infection given the data concerning protection against possible Lyme disease, that is, the categories 2.1 and 2.2 cases.

Number three, please comment on the use of Lyme disease vaccine in persons over 70 years of age. that question is straightforward on its own, as is the following one.

Number four, in the efficacy trial, vaccinations were given just before the Borrelia burgdorferi transmission season at 0 and one month between January 15 and April 25, and then 12 months later between approximately

February 15 and April 30. Should a similar seasonal vaccination schedule be recommended in the package insert?

Finally number five, are there any additional studies that should be performed by the sponsor, and we are particularly interested in comments on additional studies for rare adverse events, the duration of protection, booster doses, and pediatric stories, and some of those studies are ongoing.

We are interested in a vote from the advisory committee on questions 1, 2, and 4, that is, the safety, efficacy, and seasonality questions, and comments on questions 3 and 5.

CHAIRPERSON FERRIERI: Could you please show slide 4 again, Dr. Elkins?

DR. ELKINS: I believe that is the efficacy question?

CHAIRPERSON FERRIERI: Well you had -- the one on question one and then the target --

DR. ELKINS: Slide 2, not question 2. Is that the one? Efficacy of safety points.

CHAIRPERSON FERRIERI: This one. Any other questions on the questions?

DR. GREENBERG: I have one.

DR. ELKINS: Yes, Dr. Greenberg?

DR. GREENBERG: The safety question is literally 3 doses of vaccine given as the -- or the safety of this in other contexts with multiple -- you want to know simply safety of 0, 1, and 12 months?

DR. ELKINS: Yes, sir.

CHAIRPERSON FERRIERI: Thank you very much, Karen. We will now take a 15-minute break, and then we will come back at 4:00 for the open public hearing and then we will resume discussion and voting.

(Whereupon, at 3:46 p.m. off the record until 4:03 p.m.)

CHAIRPERSON FERRIERI: We will resume the meeting now. If the committee members would please sit down. You have in front of you the questions that Dr. Elkins flashed on the screen a few minutes ago. So we will stay with those and try to get everyone to the table before we start.

The game plan that seems most logical is for us to have discussion and then voting on the questions that the agency wanted to vote on, questions 1, 2, and 4. And within our discussion, I would like committee members to be bouncing

off each other ideas, reactions, and so on, so that we are conveying information that will hopefully be valuable to CBER, and addressing as well the addendum questions to each of the major questions.

So if we could have everyone seated again, please. I have just been reminded that I am guilty of a serious omission. We need to call for the open public hearing. The jargon is OPH. Is there anyone here? Mrs. Cherry will conduct the open public hearing. We have never had quite so many.

MS. CHERRY: We had advertised one occurring in the late afternoon. So I thought that if there is anyone here who wishes to make a comment, this is the chance. If not, I will return control to our chair.

CHAIRPERSON FERRIERI: Thanks, Nancy. So let me read the question then that you have in front of you. For the audience, are the data sufficient to support the conclusion that the vaccine is safe for immunization of individuals 15 to 70 years of age. So confining our discussion around that point, I would be happy to entertain volunteers to open up the discussion. It makes it more spontaneous than trying to go around the table. We will do

that when we take a formal vote then. Who would like to open up this question then on safety? Steve Kohl?

DR. KOHL: Well, is anyone else concerned about the two cases of paresthesia, arthritis, and the DR positives?

MS. COLE: I am.

DR. KOHL: We have two out of roughly 500, I would guess, who are DR4 positive versus zero out of 4,500. And to me that sounds statistically significant.

CHAIRPERSON FERRIERI: Thank you, Steve. Mrs. Cole -- Rebecca Cole. We have several people whose names sound familiar.

MS. COLE: I agree with Dr. Cole. There are several things that concern me. I think the question in all honesty should be rewritten a little bit because there are so many groups of people that were left out of the testing that it is really difficult to say, yes, they have proven it safe for everybody 15 to 70, because they haven't.

CHAIRPERSON FERRIERI: Please elaborate on that.

MS. COLE: Well, there needs to be certain individuals. You were talking about no former Lyme patients could have this, nobody with arthritis. They weren't included

in the testing. No cardiac pacemaker patients. There are a lot of groups of people in this country that would be left out. So I don't think you could say that it is safe for everybody 15 to 70, because that hasn't been proven.

CHAIRPERSON FERRIERI: Other reactions to this? Yes, please, Dr. Greenberg.

DR. GREENBERG: I still am concerned about the fact that from the antibody data we have been seeing, it looks likely that this vaccine may be given in more frequent administrations than just three doses in the lifetime of a recipient. So I have even more concern about if the vaccine is going to be delivered on repetitive vaccination, but I have no data to judge its safety.

CHAIRPERSON FERRIERI: Okay. Dr. Coyle?

DR. COYLE: I think that is probably a very important point. Because as the question is phrased, and the only data that we have is this three vaccination schedule. And it is very clear that that can't be how -- that is not likely to be the way this vaccine is going to be used. So I think that may come into the final question with regard to post-marketing analysis that has to be done.

CHAIRPERSON FERRIERI: Dr. Snider? Did you --

DR. SNIDER: Yes. Well, I was just going to elaborate some, which gets a little bit over into efficacy. But I think I agree with Dr. Greenberg and others that it would appear that there is a correlation between the antibody titer and vaccine failures. I didn't ask the sponsor the question directly of whether there were other correlates. Age and so forth was eluded to. We kind of skirted around it and didn't attack it directly. But I think the point is that if this putative mechanism of action is correct, what it means is that in contrast to many other vaccines, you have got to have a certain titer of antibody in your blood in order for the vaccine to be protective, which I think means repeated boosters, whether they are annual or every two years or every three years or whatever. So in terms of safety, I think what the committee is saying is we have to worry about a longer period of time than the 20 months of data we have in front of us. So we have the dilemma of how much data do we need on the table before licensure, and how much data are you willing to defer to after licensure to collect.

CHAIRPERSON FERRIERI: I think you have hit on the crux of the issue and summarized it very well. Dr. Clemens-Mann?

DR. CLEMENTS-MANN: I would just like to say that we should keep an open mind about this. I think that for certain diseases, we do have to boost rather frequently, including influenza vaccine for people that are at high risk. So if we keep that in mind. I agree that the study as designed did not include -- you can't generalize to all 15 to 70-year-olds, and that there would need to be a concerted effort made to expand the safety data to include the entire population of people who might want to be vaccinated in that age range, and that there will need to be follow-up studies to look at the safety and immunogenicity of subsequent doses. So I think -- I mean, I think these are all things that can be worked out.

CHAIRPERSON FERRIERI: Do you want to propose what would be an optimum period of follow-up to pursue those points for safety and immunogenicity?

DR. CLEMENTS-MANN: Well, I guess the -- you know, it seems to me that there is going to be a -- there is actually going to need to be more data coming to look at the optimal way of immunizing also, and that these data are being collected. So it may turn out, who knows, like hepatitis and others that you could actually immunize three

doses in a year and get a very high response, which then would tail off perhaps over a longer period of time. But I think in terms of the repeated boosting, that that data will be possible to get if they are immunized the third year and then the fourth year. At least we can look at those cohorts of people to see if there are any problems with reimmunization.

CHAIRPERSON FERRIERI: Dr. Dattwyler?

DR. DATTWYLER: I just want to say I agree with that. But getting back to the DR4 thing, if you looked at -- say it is between 10 and 20 percent of the Caucasian population. That is probably around 1,500 individuals in this study. And the sponsor said that there were two people who had an adverse event in the vaccine group and one in the placebo group. I don't think that is statistically significant.

CHAIRPERSON FERRIERI: Pardon me? You don't feel it is significant?

DR. DATTWYLER: Right. I mean I think that I would assume if that is the case that DR4 is a rather common thing. If we were going to see a widespread effect secondary to that haplotide, I would expect to see it in a greater number of people.

CHAIRPERSON FERRIERI: Dr. Clements-Mann?

DR. CLEMENTS-MANN: Yes. I guess that was my other point too. Ordinarily if it is due to vaccination, you would have expected an exacerbation when they were, as Pat said, rechallenged or reimmunized with the vaccine. So that it is unclear to me that that event was related to that second immunization.

DR. DATTWYLER: Yes, I agree.

CHAIRPERSON FERRIERI: Dr. Broome, do you agree with that? Claire?

DR. BROOME: I am just following up for a minute on this issue of the DR4 susceptibles, if you will. The -- what is the predictive value of DR4 positivity, if you will, i.e., of the folks who are susceptible, what proportion will actually have rheumatologic manifestations, and is it a tenable hypotheses that that group may have been preferentially excluded from this trial because of the exclusionary criteria?

DR. DATTWYLER: But assuming it is 20 percent in the Caucasian population, and even if you drop it down and you exclude half of those, then you would still have 1,000 people with that haplotide.

DR. BROOME: But what I am saying is that not everybody with that haplotide goes on to develop arthritic manifestations.

DR. DATTWYLER: Sure.

DR. BROOME: What is the predicted frequency with which?

DR. DATTWYLER: I don't know. I mean, I don't know the answer.

DR. POLAND: It is low. It is very low. That original association was described by work done at the Mayo Clinic, and it is apparent that it is multi-gene that are environmental effects. I can't give you an exact number, but I would be surprised if it was more than -- if it predicted more than 30 percent rheumatoid arthritis, and maybe not even that.

CHAIRPERSON FERRIERI: Dr. Fleming, how do you react to this type of loose discussion of probabilities? You have always held us to such an incredibly high standard. This must be really disappointing. He is thinking. Mary Lou again, please?

DR. CLEMENTS-MANN: I guess one of the things we can't really answer in this study is what would happen to

people who had the right -- who had the unfortunate allele who were vaccinated and then developed subsequent infection, maybe one of these milder ones that didn't get treated. And that would really be something that would have to be looked at, I think, under a totally different study design. It is not clear to me that the vaccine itself, at least based on the data we have seen, elicits this kind of adverse event, the chronic arthritis. And it may well be that it is really associated with the actual infection, which is more than just that one antigen exposure. So that that to me is going to be a separate question of whether the combination of vaccination and infection that would occur when it is used on the wide scale without the surveillance could occur. And that would be another important question to look at in terms of safety.

CHAIRPERSON FERRIERI: Yes. Dr. Snider and then Dr. Hall.

DR. SNIDER: Well, just to try to get back to the question and not dance around it as much. I agree with Mary Lou that we don't know for a fact that the vaccine has elicited any of these -- either one of these episodes of arthritis and paresthesias, but I think we are all worried about that. But when the question about safety is raised, it

is always a relative term. And in this artificial environment of a clinical trial, we look at the placebo recipients as a comparison, but they really aren't going to be the comparison group in the real world in the sense that folks are not going to be followed so carefully. So, in fact, there will be in reality, I would suspect, cases in which EM occurs but it is not recognized, and so arthritis and neurologic effects occur. And this is what in the real world we have to balance against when we talk about the safety of the vaccine. It is the relative safety. And that is difficult for us to do because we don't have or at least I don't have the numbers from what happens in the real world of people who are not monitored in the context of a clinical trial.

CHAIRPERSON FERRIERI: Dr. Poland, did you have your hand up?

DR. POLAND: I was just going to say in regard to the DR question, that is a Phase V study. It is just not going to be done, I don't think, pre-licensure. On the other hand, there probably is an animal study you could do where you could hyperimmunize human transgenic mice that carry the human DR4 allele, and that strain exists. And furthermore, they have a -- you can induce a syndrome very similar to rheumatoid

arthritis and Lyme disease in them. So that may bear worth looking into.

CHAIRPERSON FERRIERI: Good idea. Dr. Fleming?

DR. FLEMING: When I look at the safety issue, I am inclined to break it out as to short term and long term. And I think the study conducted as it was in a high quality fashion has I think informed us quite a lot about short term. And what is apparent in short term as I see it is some level of safety, but relatively small. We see under solicited symptoms a 5 percent increase in rash and arthralgias, for example, which aren't irrelevant but they are generally of tolerable levels. Dixie raised the issue about whether or not -- and I think a very important issue about whether or not the control here really is a real world control. I will come back to that a little bit more when we talk about efficacy, because it may be that we are missing some of the efficacy because we are delivering a placebo that is really more than a real world intervention, as you point out, because of the careful follow-up that we have and antibiotic use. On the safety, of course, that may mean that we are covering some of the safety differences because we are intervening more in the placebo arm than we would in the real world.

In terms of my more substantive concerns here, they are relative to the longer term issues. It is somewhat reassuring to hear the discussion that we heard just before the break that if there are safety issues or safety concerns that are, for example, manifest in terms of chronic arthritis, that we should be able to detect those. I remain, though, somewhat concerned that if we had been in the position where we could have had a longer term follow-up in larger numbers, which I am not necessarily advocating because there is a limit to how much we can request pre-marketing. But I am left with uncertainties about whether there really are, and maybe these two cases of paresthesia that we are seeing are in fact a signal of something that we would have seen if we had been able to follow longer. So I am left with uncertainties on that regard.

And then the other issue that has been raised is will there need to be booster doses. And if we just look at the second year experience from the first year experience, there certainly is a clue that the higher GMT levels that we have in that second year, which range from 10,000 to 1,000 as opposed to 1,000 to 100, i.e., the GMT levels are ten-fold higher in the second year and protection is 80 percent rather

than 50 percent. So there certainly are some clues that there may well need to be consideration of maintaining proper GMT levels and there could well need to be additional boosts. And obviously that would then require subsequent follow-up for safety issues that haven't been answered here but presumably would be answered in subsequent trials or post-marketing surveillance.

CHAIRPERSON FERRIERI: Thanks, Tom. Other discussion? Dr. Edwards?

DR. EDWARDS: I think we have been talking a little bit over here in this corner about issues related to the peripheral nerve or joint findings on one side, unilateral. Is there any possibility that these are related to the injection, like a brachial neuritis or something else? Because it seemed like at least in one of the cases that all of the symptoms were occurring on the same side as the injection. I guess -- is there any more information --

CHAIRPERSON FERRIERI: Is there any more information on this issue? Does anyone -- Dr. Steere, you might be the best to respond to that.

DR. STEERE: Well, Vijay, you may want to comment on this more. But the patient's EMG was normal. So,

in other words, in terms of explaining it as a brachial neuritis, I don't think it was a brachial neuritis.

DR. EDWARDS: But the patient had an injection in the left arm and then all of the symptoms were in the left upper extremity?

DR. STEERE: Yes, following the second injection. Do you want to comment?

DR. SIKAND: I can just echo and reinforce. Indeed, she had the injection IM in the left deltoid, but her symptoms were in large joints of the left upper extremity. And the paresthesia were indeed in the left upper extremity, but she had nerve conduction studies which were completely normal.

DR. EDWARDS: And the other patient that received vaccine and had the paresthesias, was it very much the same in the same arm?

DR. SIKAND: That was not my patient.

DR. STEERE: No, that was not. That patient had symptoms in all four extremities.

CHAIRPERSON FERRIERI: Thank you. Further discussion on safety in this age group? Dr. Hall?

DR. HALL: I guess there are two parts of this.

I think at this point we have little evidence that the vaccine itself causes any long-term or more serious adverse effects. I mean, I have not seen the data in terms of the adverse effects except less than 30 days and over 30 days. But I would imagine that most of these occurred in the first couple of days. And if it didn't or if there were differences according to the adverse effect from the first few days to the latter days, that may give you some clues. But at this moment, it doesn't seem that we have much evidence for any long-term effect. And the second question then that come up is hyperimmunization as has been raised and the safety of this, and that with the additional doses that are so far obtained or has been given, there is no more and in fact less in terms of the adverse events. So the question really is in terms of booster doses is not one to me at this point so much of safety as of protection and that whether that decline is going to be as rapid as it may look after the second year and require a vaccine later. But if you redefine this question as are data sufficient to support the conclusion that it is safe for immunization of individuals 15 to 70 years of age over a period of two years -- if you time limited it, then that may be an easier question at this point to answer.

CHAIRPERSON FERRIERI: It is my understanding that that is the question that we are addressing. Or not, Dr. Elkins? Can you respond to that briefly?

DR. ELKINS: Yes, that is the question. Our expectation is that since the indication for this vaccine would be a 0, 1, 12-month schedule, that we are interested in comments on safety data assuming that schedule use or any variation thereof. That is, some patients may receive only one dose and some only two and so forth.

CHAIRPERSON FERRIERI: Thank you. Dr. Dattwyler?

DR. DATTWYLER: Can I ask a quick question then? Does that mean that the sponsor will have to come back for approval for additional booster studies and give additional data to get approval -- say a 24-month booster or a 36-month booster or something like that?

DR. ELKINS: Yes. The current indication would be a stands and any variation on that would need a supplement to the license application.

DR. DATTWYLER: Because one of the points I was going to make later on for question 5 is I think additional studies are absolutely mandatory to look at the effects of

boosters and additional immunization schedules.

CHAIRPERSON FERRIERI: Thank you, Dr. Dattwyler. We will pursue that when we get to question 5. Any brief points here? Bob? Dr. Daum?

DR. DAUM: I am not -- Bob is fine. I am not sure that I heard very much about lot to lot variation in terms of safety considerations. And I don't know if that is going to turn out to be an issue or if the data are there and presented and I missed them or if the data really aren't there yet. But there are certainly other instances where there are different safety profiles and different lots of other vaccines that many in this room are well aware of. So that is one issue that I would -- I was going to save that for immunogenicity issues, but it comes up under safety also.

CHAIRPERSON FERRIERI: Yes. Dr. Finkelstein?

DR. FINKELSTEIN: Just one other point. It seems like this is a broad range of ages, and I am not sure that there is very much data in the low age range or the very high age range. So it would seem that it would be valuable to get more of that. Not necessarily prior to marketing, but eventually it would be useful to have that information.

CHAIRPERSON FERRIERI: Thank you. Dr.

Greenberg?

DR. GREENBERG: I just want to bring up that safety is twofold. One is the possibility that people will receive many more doses of this vaccine, and so we really haven't seen what multiple dosing is like. On the other side, people will be vaccinated with an initial vaccine regimen and then go perhaps for a number of years and not be vaccinated and then become susceptible if the decline. And the question is in that case where you might have T cells that are sensitized and not be protected, will there be an altered response. For sure that doesn't happen within the context of this 12-month experiment, and I don't see any way to get around that. But given the immunologic nature of this disease, that is a worry long-term, and it is more of a worry than many other types of infectious disease.

CHAIRPERSON FERRIERI: Are there additional preclinical issues that you would want addressed regarding this question? Is there any more preclinical data that you would want? Dr. Karzon?

DR. KARZON: The safety issue here seems to me to be very complicated compared to any vaccine I know that has been licensed. And we have unearthed the -- those who did the

trial have unearthed some very interesting sinister possibilities that may or may not be real. One is that we have excluded people with arthritis. I don't know what percentage of arthritics have been excluded, but that is a group that has been a part of the trial. And we can make the judgment that the arthritis is not a threat and we don't have to explore it any further, or we can say since this hasn't been done, we can make this a clinical trial.

One of the problems I had or questions we can ask the manufacturers is whether they can initiate in any way a trial to answer further questions. And the possibility exists since the original exclusion has not been satisfied -- we still don't know theoretically whether arthritis patients will get into more trouble if they are vaccinated or not. So we could divide those into two groups and therefore have a valid placebo study. I don't know the reality of that suggestion itself, but it exists as a possibility.

We have said that we have excluded them. We have no data on it. And we can now say that to include them again, they need to be studied. How much or how long or in what way, I think we probably know those pathways.

There is a couple of other safety things that

we don't know all the answers, and one is problems in AV function. As people get older, and we are going to have more people in this age group who will take this vaccine, AV dissociations are going to become more common. We don't know what impact the vaccination has on that system. We have some data. Maybe we need more data. And then something that has nothing to do with safety, but in a way it does, and that is how many further doses we need. We know that the half-life of antibody is short after one dose. The half-life from the curve shown may be a little flatter and maybe a little longer after the second dose, which would fit as a physiological antigen administration. But we really don't know when and how many doses should be given and whether they offer any safety issues to be, if you will, hyperimmunized.

Another safety issue that is there but unresolved is the very interesting studies that Dr. Steere did to show what seems to be an autoantibody response. That, I think, has been very nicely pursued, but we don't know the final answer to that. We don't know the significance of DR4 in a statistical sense.

I see a lot of reasons why we have a lot of unsprung threats. I don't know myself how to best follow

those -- what sort of follow-up we need for safety. And as I said earlier, rare events will become common when a million people are vaccinated. Furthermore, I can see all kinds of accusations or allegations of injury that aren't real in this sort of setting, and we have to clarify what is real and what isn't real. If somebody develops arthritis, well blame it on the vaccine. That is easy. But the big question I have in my mind is we need follow-up. How to do it is very difficult. I would like to hear others opinions about how this could be done and that is realistic for the manufacturer. I am sure they are just as interested as anybody else to make sure their product is safe and sound and know all the contraindications and things that should be watched for.

CHAIRPERSON FERRIERI: Thank you, David. Those are very sobering thoughts and analyses. I don't see that we have better answers that have emerged from the table. There is a desire to try to balance a very reasonable response and analyze the data very rationally, but we heard emerging from several people at the table their concerns. No one has yet suggested that we have extension of the follow-up on the studies that have already been executed or that are in trials. Is there anyone who wants to add to what David has said? I

might add for the agency that several of us spoke in the corner a few minutes ago and thought that it would be reasonable to propose a sub-trial, if you will, in patients with chronic arthritis or joint disease, where you would know up front their DR status and that you would have vaccinees and placebo controls who would be followed for a very long period of time, much beyond the time follow-up in the current 008 study. So that is something very specific that we can offer up to you, Dr. Elkins and other members of CBER.

But regarding Dr. Karzon's question to us committee members, should we require longer follow-up before we can really endorse the safety in this age group, or do you feel more sanguine? There may be quite a bit of dissention among the table. How do you feel, Dr. Dattwyler?

DR. DATTWYLER: Well, unfortunately I think it is like buying a computer. You know that there is always going to be something better next month, and the question is when to jump in. I am not sure. I think that they have done a very nice study that has shown that in this 20-month period in this population that there is a reasonable degree of safety. But the long-term effects of repeated immunizations and what is going to happen in subpopulations I think is

something that needs to be studied. Can that be reasonably done as a post-licensing study or does that withhold licensing? That is a tough question and I am not sure I know the answer to that. My overall probably answer to the question is, yes, there is enough there based on the data they supplied and then it becomes the agency's problem as far as what appropriate things to do are. So I am not -- I am hedging, obviously.

CHAIRPERSON FERRIERI: Well, the agency can come back to us, and we will be pursuing this in question 2. If we have more boosters, then we are going to need longer follow-up of that group certainly. I think we need to cut loose here. One last comment, and then we are going to vote on the precise question. Dr. Clements-Mann?

DR. CLEMENTS-MANN: I guess in the ideal world, it would be nice to follow vaccinated and placebo people for a very long time, but I don't think that that would altogether be ethical. If you indeed are withholding a vaccine that would prevent the possibility of Lyme disease and would then avert some of these chronic conditions. So that I think it might be unreasonable to have a fixed placebo group for a long period of time. And that what would be nice is to follow this

group 1- as many of the people in this trial for breakthrough cases 2n the future. Because they are going to get varying numbers 3 of immunization boosters and so forth. To begin to unders4and what level of antibody makes them or decline makes them su5sceptible, and then what kind of disease occurs. It may be 6that there is more modified disease in the vaccinated or it m7ay be enhanced, and that would be important inform8tion.

9 CHAIRPERSON FERRIERI: Thank you. We will start 10voting then -- yes or no or abstain. Starting with Dr. Dattwy11ler.

12 DR. DATTWYLER: Yes.

13 CHAIRPERSON FERRIERI: Dr. Coyle?

14 DR. COYLE: Well, I vote yes with the proviso that 15is is for a single cycle of three vaccinations. I can make 16 comment on the people that were excluded and I have a questi17n mark about the elderly.

18 CHAIRPERSON FERRIERI: Fine. Dr. Luft?

19 DR. LUFT: I vote yes with a similar proviso as well as 20 the group in regard to rheumatological conditions.

21 CHAIRPERSON FERRIERI: Thank you. Dr. Broome?

22 DR. BROOME: Yes with the same provisos. And I

guess I think it is important to note that it is not going to be trivial to figure out what do you do about the ones that were excluded. I think that the endpoint we are talking about is common enough and poorly defined enough in terms of chronic arthritis that use of the vaccine in populations that were excluded from the trial is going to be difficult to assess.

CHAIRPERSON FERRIERI: Dr. Breiman?

DR. BREIMAN: Yes. And I guess we should just agree on the proviso, so we don't all have to say the same thing. But the one thing I would add to that, though, is that -- and I think Mary Lou may have mentioned this, but one thing that hasn't been talked about in great detail is the implications of vaccinating a patient that is currently infected or just has been infected within the last few weeks, which would have been another excluded criterion. But given the autoimmune issues and the possibility that there may be sort of antibody bug relationship there that could contribute, that is a concern too. And again, I am not sure how one would study that.

CHAIRPERSON FERRIERI: Dr. Eickhoff?

DR. EICKHOFF: The same provisional yes. I think my provisional relates to people with chronic arthritis

and people with other serious underlying diseases who are clearly less likely to be exposed in the first place, and people who are beginning to approach that upper limit of age 70. I am not sure I have a good feel for the efficacy data by the time we get to the 65 to 70 age range.

CHAIRPERSON FERRIERI: So to summarize up to this point, these provisos that we are imposing and leading to provisional affirmative voting includes such issues of age, the data at the two ends of the spectrum, patients with arthritis, the suggestions earlier of special studies zeroing in on this age group as well as the other exclusions that have been mentioned regarding the recent infection. Dr. Fleming?

DR. FLEMING: Essentially similar provisos. Yes, short-term safety is established in those who met eligibility. So obviously additional information is needed in the chronic joint disease cohort and others who were excluded. We will talk about that in question 5. I would also say that this yes is also conditional on the duration of follow-up. So I remain with non-trivial concerns about whether the vaccine could be eliciting or inducing chronic infection over an interval of time that would not have been detected with 12 to 20 months of follow-up. And again in question 5 we will come

back to additional studies.

CHAIRPERSON FERRIERI: Did you mean chronic infection or chronic sequelae?

DR. FLEMING: Chronic sequelae -- excuse me, chronic arthritis or chronic sequelae. I am sorry I misspoke.

CHAIRPERSON FERRIERI: Fine.

DR. FLEMING: And obviously as well if there are different booster schedules, et cetera, that would have to be assessed for safety subsequently.

CHAIRPERSON FERRIERI: Steve Kohl?

DR. KOHL: Yes with all those provisos.

CHAIRPERSON FERRIERI: Dr. Karzon?

DR. KARZON: Yes. I can't imagine doing much better than these individuals that presented this today have done with a very difficult problem. So we have learned an extraordinary amount and I like it. But if we ever needed an intensive follow-up, call it Phase IV if you will, which has been worked over carefully and prescribed, that should be appended to that approval.

CHAIRPERSON FERRIERI: Absolutely. Mrs. Cole?

MS. COLE: My vote is yes also, but as everybody else has stated just limited to the groups that were

tested in the trials that as far as I am concerned the safety is proven in. I would want to see a lot more work done on this.

CHAIRPERSON FERRIERI: Dr. Daum?

DR. DAUM: At the risk of being a little bit repetitive, yes, with the proviso that has gone all the way around. But I would also like to point out that it is my sense from hearing the discussion that almost certainly this vaccine is going to require additional dosing than the schedule that was used in the study. And thus I would like to put an additional proviso on that I think it should be evaluated, whether 4, 5, or 6 or who knows how many doses is equally safe or generates similar kind of data to what we have heard today.

CHAIRPERSON FERRIERI: Dr. Finkelstein?

DR. FINKELSTEIN: Just a couple of other provisos. One is that I would sort of -- I would like to have the age range actually shrunk in terms of something of the nature of 20 to 60, because there is not that much in the other extremes, and there is possibly -- especially in the elderly, it is possible there are side effects. And also just to point out that this is not that large a trial. So that

some of the more rare side effects or complications wouldn't show up in this. So there is that aspect of it.

CHAIRPERSON FERRIERI: Dr. Clements-Mann?

DR. CLEMENTS-MANN: I agree with all of the provisos, except I don't agree with the lower age range. I see no difference between a 15-year-old and an 18-year-old, and there have been over 300 people enrolled between 15 and 18. I do have the concerns about the older age group as have been mentioned.

CHAIRPERSON FERRIERI: Dr. Greenberg?

DR. GREENBERG: I vote yes, and I am not sure this proviso has been thrown out. But this vaccine has the potential to be like the inactivated measles vaccine, and that is to cause a late unanticipated event in people who were vaccinated with a different disease. So there needs to be very careful monitoring, even if there is no boosting of people over time -- over 5 and 10 years to make sure that they don't respond to a secondary infection in a different way.

CHAIRPERSON FERRIERI: Dr. Hall?

DR. HALL: I would also vote yes and the provisos seem reasonable. But I think also we should be realistic that in the real world these provisos are probably

not going to be very well adhered to. And particularly -- I can't find the entire list that I saw earlier of all the various exclusion criteria, but I think that would include a great many people in our population, and I am not sure that that would be warranted even.

CHAIRPERSON FERRIERI: Dr. Snider?

DR. SNIDER: Well, like others I am not completely sure about the absolute long-term safety. But I will vote yes based on relative safety compared to the risk of people in endemic areas going unvaccinated. So I think the benefits are on the side of vaccination, at least in the short term. And as mentioned, we don't know in the long-term. And again I would emphasize, as others have, that although it is difficult, this seems to me to be one vaccine where we are going to have to find a way to do long-term follow-up. Because it appears that not only are we going to have to be concerned about chronic sequelae, but the potential need for more than one booster dose. One aspect of the exclusions that people haven't mentioned that is troubling to me has to do with -- I understand why I think certain groups were excluded, but it creates for me not only a practical problem but an ethical problem. And particularly with regard to children who

are at high risk of disease. So I have to wonder what we are -- I mean, I know fortunately a trial is underway. But what is the ethics of making a vaccine available to certain select parts of the population and not other deserving parts of the population who are at risk. So for me it is a lesson of when thinking about designing trials to think about those aspects as well.

CHAIRPERSON FERRIERI: Thank you, Dixie. Dr. Huang?

DR. HUANG: I certainly vote yes, and I also support the extension of the vaccine to people 15 years of age.

CHAIRPERSON FERRIERI: Dr. Edwards?

DR. EDWARDS: I support this. However, I do have some concerns. I think that we need to very carefully follow these individuals. We need to extend at both ends and both age spectrum additional studies and we need to pursue the long-term follow-up very carefully.

CHAIRPERSON FERRIERI: Dr. Poland?

DR. POLAND: Yes, subject to the provisos that will come up in question 5.

CHAIRPERSON FERRIERI: My vote is yes with

great ambivalence and also in support of the provisos that have been mentioned with emphasis on the need for long-term follow-up and additional studies. I might comment that this is fairly rare for a vaccine to be voted on with so much ambivalence by everyone with a stack of provisos. Dr. Hardegree would be able to confirm whether or not this is relatively unprecedented. So that is all for the formal vote. I would like to throw out to the committee before we move on to question 2 the issue of use of Lyme disease vaccine in those with a previous history of Lyme disease and would like some of you to reflect back on the comments made earlier from the sponsor regarding the risk of second infections and the susceptibility

-- the alleged susceptibility of people who have had one attack of Lyme disease and their susceptibility to second infections. That is not universally accepted and there are clinicians in the audience who consider that a relatively infrequent event. So what is the committee's reaction to this and the use of it in patients with a previous history? Do they need so much more protection by undergoing a vaccination series? Who would like to lead off on that? Dr. Dattwyler?

DR. DATTWYLER: I think that is an issue that

has to be studied very rigorously. If one looks at the question of autoimmunity and arthritis, it may be that the demure of having the bacterium in the joint is necessary for the development of significant chronic arthritis. And if you have that and you prime the T cells with this vaccine, you might cause some difficulty. So I think that that would be -- and I was going to address that in question 5. But that, I think, needs to be studied quite rigorously.

CHAIRPERSON FERRIERI: Thank you. Other committee responses to this? Is there some consensus? A nodding of heads or hands on the further studies on this? Please don't fall apart now. We are only about a fourth of the way there. Whatever it takes. We will stay as long as we need it. If we could push ahead. Dr. Hall and then Dr. Luft.

DR. HALL: I am a little confused about the data that was presented that there seemed to be more unsolicited musculoskeletal events in those who had a history of Lyme disease, but that was not so in those who had confirmed serologic previous disease. Is that correct?

CHAIRPERSON FERRIERI: Sponsor? Is that correct?

DR. PARENTI: Yes.

DR. HALL: And for those events, what are those musculoskeletal events that were in the unsolicited only in those that had a history but not confirmed?

CHAIRPERSON FERRIERI: Dr. Parenti?

DR. PARENTI: Those are the same events that we saw in the vaccine. In other words, vaccinees had the arthralgias in the first couple of days that were transient and mild, and that was seen in the people who had previous Lyme disease population. We saw the same effect in the people who had Western blot positive. Again, vaccinees had the same short-lived arthralgias. So that accounts for the early events of arthralgia that I believe were the only differences between the groups.

CHAIRPERSON FERRIERI: But were they greater?

DR. PARENTI: In the people who were Western blot positive -- if you compare the Western blot positive people to the Western blot negative people who were vaccinees, no they were not greater. There was no difference in that population. If you compare the people with a previous history of Lyme disease to other vaccinees who did not have a previous history of Lyme disease, they were greater. However, if you also look at the previous history of Lyme disease people who

were placebo recipients and compare them to previous Lyme disease -- oh, I am sorry, to their counterparts, people who did not have a previous history of Lyme disease and got placebo, you also had a higher incidence of events. So the people who had previous Lyme disease by their history, whether they received vaccine or placebo, had a higher rate of events. And that includes not only musculoskeletal. They had GI. They had psychiatric complaints as well.

CHAIRPERSON FERRIERI: What does that tell you?

DR. HALL: How can you explain that. But if they had confirmed, that does not follow. I mean what is the dichotomy?

DR. PARENTI: I don't know if I want to throw out a hypothesis on that except that that is what the data were.

CHAIRPERSON FERRIERI: Okay. Thank you. Any other thoughts on this issue very briefly?

DR. LUFT: I think I would like to go back to a remark that Dr. Poland made and that is actually the power of being able to make any assertions in regard to these various subgroups. It is only about 2 percent of the patients who were vaccinated that had Western blot confirmed prior

disease, and that is about 100 patients in total. And if you look at that group of those patients that possibly could be DR4 positive, you are now talking about 10 to 20. It is a very small number. And I just have to recall what Allen Steere proposed as part of the pathogenetic mechanism. I don't think we have the numbers to say that there is real safety within that group. It is just too small of a group. I don't think we have the

-- so I have some real reservations about using this vaccine in people who have had prior Lyme disease.

CHAIRPERSON FERRIERI: Thank you, Dr. Luft. I also share those concerns very much. Other responses from the table on this issue -- this subtext. Dr. Coyle?

DR. COYLE: I'll just mention that it is also going to make potentially diagnosis of vaccine failures more difficult.

CHAIRPERSON FERRIERI: Other reactions from the committee? Dr. Steere, did you want to add a point of information on this issue?

DR. STEERE: Well, the only thing that I was going to say is that self-reported Lyme disease may not be Borrelia burgdorferi infection.

CHAIRPERSON FERRIERI: That is hard to dispute. Dr. Koval, did you have a point here? Otherwise, I think we should move on if we are going to accomplish the rest of the agenda. We have on the screen as well as in front of you the second question. Are the data sufficient to support the conclusion that the vaccine is effective? So we are dealing now with efficacy against definite Lyme disease in individuals 15 to 70 years of age when given on this three injection schedule of 0, 1, and 12 months. So we can open up discussion here on overall efficacy in this age group with this schedule, and then we have one other major point to discuss. Dr. Finkelstein?

DR. FINKELSTEIN: We might be able to avoid some of the provisos we have in question 1 if we could start by saying limited to the study population, in other words all the exclusions that were involved in this particular study. At least this time the question does have a schedule, but it also doesn't say excluding the following populations.

CHAIRPERSON FERRIERI: Discussion first. Everyone is speechless. Dr. Greenberg?

DR. GREENBERG: I think this answer will be pretty clear, but maybe I am misjudging the rest of the board.

CHAIRPERSON FERRIERI: Yes. I think I see a lot of heads shaking affirmatively. Does anyone want to add anything here or feel confused about the question? Yes, Steve Kohl?

DR. KOHL: For all of my negative comments, I think we need to congratulate the group that did this study. It is a fairly impressive and extremely well carried out study. And not only has it taught us about the vaccine, but it has taught us a lot about Lyme disease.

CHAIRPERSON FERRIERI: Indeed, yes. Dr. Breiman?

DR. BREIMAN: I guess I was just wondering about -- getting a little pickyunish here and focusing on that actual age range of 15 to 70. Do we have enough information about the upper end there to say that it is efficacious in the older to 65 or even the 60 to 70 age group?

CHAIRPERSON FERRIERI: Well, that is a concern of several people at the table and that has been voiced on more than one occasion. Dr. Daum?

DR. DAUM: I guess the question is posed in an appropriately narrow way that allows at least me to answer with probably yes. On the other hand, I wasn't very

overwhelmed by the data that showed the two-dose efficacy, hereby presented as the first year efficacy. So it sounds like I guess the first point I would like to make is that it really looks like that third dose seemed very important. It also seems like it is really dependent almost exclusively on one modality. The response to the vaccine, which is the amount of circulating antibody you have. I mean, I really had the feeling that you've got to have antibody or you just become susceptible again. And you also have the feeling based on the response to wild type infection in terms of anti-OspA antibodies and also in terms of the very rapid decline of antibody with what almost seems like no goosing in the middle that there is not going to be a lot of I guess stimulus by antigens circulating in the community to existing immunity. So it is a vaccine that is really -- it is immunity that is predicted on having sufficient antibody. And it sounds like, at least based on what I have heard today, that it is pretty likely that that has got to be provided by the vaccine itself. I don't think we are going to get a population phenomenon with this vaccine because I don't think it is ever going to have the kind of coverage -- I may be wrong -- that you might think would produce that. And also because there are such huge

animal reservoirs, and I don't think that we are the major source of organisms or the major target of infected ticks. So that I don't think the organism is going to be eradicated and it is really going to depend on -- the continued effectiveness of the vaccine is going to depend on the continued personal maintenance of antibody. I am trying to think of other situations where that is absolutely true with the organism circulating at very high levels like I guess this one would. I am hard pressed to think of one quickly where that is true.

CHAIRPERSON FERRIERI: Varicella at times. And that is an unresolved issue in terms of long, long-term immunity. Dr. Edwards?

DR. EDWARDS: I think we -- I haven't seen and been able to study carefully any breakdowns of the various decades. We saw an overhead that was shown that went over that, but frankly it was a little hard for me to se. So I feel a little bit hindered in my ability to look at the immunogenicity of each decade because I don't think we have had time to study that. Maybe that would be something that the FDA with that data could very carefully focus on. If a protective level is determined, then see how many people in each age group fall into that and help in that way. But I

think we haven't been able to study the data to address it perhaps as well as we should.

CHAIRPERSON FERRIERI: Excellent suggestion. Dr. Elkins, do you have anything to add to the pool of information on this to allay the concerns that have been indicated about the age limits here?

DR. ELKINS: No, except that it bears mentioning that the efficacy analysis was prospectively defined as 15 to 70 year olds. So post hoc analyses by decade, for instance, are just that, post hoc.

CHAIRPERSON FERRIERI: Is there -- yes, Dr. Luft?

DR. LUFT: Well, I think one of the other issues is that there really has been a failure of being able to identify the protective antibody. I mean the issue regarding the elderly was that actually they had the same GMT or that it was not statistically significantly different than the younger age groups, yet there is a feeling amongst us that perhaps they are more susceptible toward disease. And I think that that is a major hole, both currently as well as in regard to booster mechanisms. When people will be boosted and whether they will be boosting neutralizing antibody or non-

neutralizing antibody. And I think that is something of concern.

CHAIRPERSON FERRIERI: Would you be suggesting that post-licensure, if it were licensed, that people in this age group would be followed for a longer period of time? That those who are already enrolled in one of these studies would have ongoing?

DR. LUFT: Maybe that would be wise.

CHAIRPERSON FERRIERI: Dr. Broome?

DR. BROOME: I actually think -- I am not as pessimistic as Dr. Luft about the possibility of defining an approach to a protective live. I think if you look at the reverse cumulative distribution curves, you can clearly see differences in attack rate by difference in post-immune antibody level. So that I think whether you use 500 or 1,000, you can at least make an approximation of what may be protective, and I think that will help in looking at the age groups. I am sure there is not enough cases to look at protection by age, but I think you can get a better cut at immunogenicity by age.

CHAIRPERSON FERRIERI: Someone else along here have a hand up? Dr. Fleming and then Dr. Finkelstein and

DR. FLEMING: Well, I think the study has certainly shown efficacy relative to the defined endpoint of definite cases. Looking at what this means or looking at where the signal is coming from, it is clear that there is a reduction of erythema migrans, interestingly at a level that does seem to relate to overall antibody level at least confounded by year with 50 percent and then the second year 80 percent. There is also a reduction in asymptomatic, although I have a harder time understanding what clinically that will mean for the patient.

Where I struggle here is related to Dixie's earlier observation about the nature of the control. When I think of the disease here, my understanding is our intention is to have a vaccine whose effect is more than preventing a rash or preventing EM. It is to prevent the overall sequelae of Lyme infection and those sequelae include the early disseminated disease and the late Lyme disease. And we have looked at, for example, a myriad of information on the joint symptoms within a month. There were 107 of those in year one and 324 of those in year two. And we were looking at those from a safety perspective and seeing no difference. But if

you also look at it as is there any evidence from an efficacy perspective of reducing disseminated infection manifest through these phenomenon, we see no difference. And so I am left with the observation that there is a clear message that I am reducing EM and asymptomatic disease but with no direct tangible evidence of a number of these other sequelae that are admittedly not common, but I would think those that could be very significantly of greatest interest. And we are left then with a point that Dixie was making. It may be that either those sequelae occur later in time or maybe they would occur within the 12 to 20-month period, but the control here wasn't really real world. The control here was more intensive follow-up and antibiotic management that maybe itself carried benefit to eliminate some of those other. So we didn't see an excess in the placebo arm.

CHAIRPERSON FERRIERI: Right. Exactly.

DR. FLEMING: We are left with speculation. Was it in fact that we did prevent more than EM but the placebo did as well because it wasn't real world or are we preventing EM without any certainty that we are doing more, that at least many of us would think would be of real clinical importance?

CHAIRPERSON FERRIERI: Dr. Finkelstein?

DR. FINKELSTEIN: Just one comment, which is when you are dealing with something that has an efficacy of say around 50 percent, like you do for the first year, I have some concern about people changing behavior if they feel that they are protected by a vaccine.

CHAIRPERSON FERRIERI: Please use the microphone.

DR. FINKELSTEIN: I have concern about people feeling that they are protected by a vaccine and therefore changing their behavior and being less careful, and prevention is important with this disease. So just making the point that in the first year the 50 percent efficacy would draw some concern with respect to that.

CHAIRPERSON FERRIERI: Dr. Snider?

DR. SNIDER: Well, Tom has already made a couple of my points.

CHAIRPERSON FERRIERI: Fine. Then we won't repeat them.

DR. SNIDER: But in getting at some of the particular issues for discussion -- what is the appropriate description of overall efficacy results and particularly the

demonstration of protection against asymptomatic infection given the data concerning protection against possible Lyme disease. I think these are important issues. Again, I agree with Tom that the clearest message has to do with protection against definite Lyme disease as measured by EM, of course with laboratory confirmation. I am still a little bit perplexed about why in the second year the number of such cases increased in the placebo group but the possible category in the asymptomatic sero conversions remained the same. That still defies explanation as far as I can tell.

But in terms of wanting to use those data, and particularly it would be tempting to want to use the asymptomatic sero conversion data to talk about efficacy, I have some concern about using category 2 or 3 in the context of this study because of the uncertainty about specificity in category 2. And even, I suppose -- I am not sure what category 3 means in the context of staying the same from season to season while definite cases go up by 50 percent. So I think the safest thing to do would be to go with the definite cases. I think that is where I would have the highest level of confidence in the data. The numbers are obviously smaller too in category 3.

CHAIRPERSON FERRIERI: Well, that is the question, the effectiveness against definite Lyme disease. And I wonder if we could have some assent to moving ahead and having a formal vote now. This time we will start on my right-hand side with Dr. Poland. Yes, no, or abstain.

DR. POLAND: Yes.

CHAIRPERSON FERRIERI: Dr. Edwards?

DR. EDWARDS: Yes.

CHAIRPERSON FERRIERI: Dr. Huang?

DR. HUANG: Yes.

CHAIRPERSON FERRIERI: Dr. Snider?

DR. SNIDER: Yes.

CHAIRPERSON FERRIERI: Dr. Hall?

DR. HALL: Yes.

CHAIRPERSON FERRIERI: Dr. Greenberg?

DR. GREENBERG: Yes.

CHAIRPERSON FERRIERI: Dr. Clements-Mann?

DR. CLEMENTS-MANN: Yes.

CHAIRPERSON FERRIERI: Dr. Finkelstein?

DR. FINKELSTEIN: Yes.

CHAIRPERSON FERRIERI: Dr. Daum?

DR. DAUM: Yes, for the duration of the study

period observation.

CHAIRPERSON FERRIERI: Thank you, Bob. Mrs. Cole?

MS. COLE: Yes.

CHAIRPERSON FERRIERI: Dr. Karzon?

DR. KARZON: Yes.

CHAIRPERSON FERRIERI: Steve Kohl?

DR. KOHL: Yes.

CHAIRPERSON FERRIERI: Dr. Fleming?

DR. FLEMING: Yes, for EM. But the study design with the placebo as it was I think did not allow us to assess whether there was efficacy relative to the other key aspects that are sequelae of Lyme disease.

CHAIRPERSON FERRIERI: Good point. Dr. Breiman or Dr. Eickhoff, sorry.

DR. EICKHOFF: Yes.

CHAIRPERSON FERRIERI: Dr. Breiman?

DR. BREIMAN: Yes. But the dosing interval may not be optimal. Of course, you are not asking that question.

CHAIRPERSON FERRIERI: We are not asking that, but we will get to that point. Dr. Broome?

DR. BROOME: It still means yes for after 3

doses?

CHAIRPERSON FERRIERI: Yes, that is correct. Dr. Luft?

DR. LUFT: Yes, I concur with Dr. Kohl.

CHAIRPERSON FERRIERI: Dr. Coyle?

DR. COYLE: Yes, as definite Lyme was defined for the time period.

CHAIRPERSON FERRIERI: And Dr. Dattwyler?

DR. DATTWYLER: Yes, with the suggestion that there be a warning in the first year that it is only 50 percent efficacy.

CHAIRPERSON FERRIERI: Okay. And for the record, my vote is yes as well. There is a subtext to this question that we can maybe deal with briefly because so many of you have made comments on it. And this is the protection against asymptomatic infection, 2.1 and 2.2. 2.1, as you might remember, was EM without any laboratory confirmation of Lyme disease. And 2.2 was a flu-like illness with Western blot sero conversion. Any further remarks against this? I think we have heard concerns about the interpretation of this category and confounding this interpretation is the meaning of the Western blot data and whether they are -- are they false

positives or not? The issues of possibly other tick-borne diseases. Dr. Daum, did you want to comment on this?

DR. DAUM: I think I would rather listen first.

CHAIRPERSON FERRIERI: There wasn't anything of substance said, perhaps. But for those of you who were listening, would you like to say anything?

DR. DATTWYLER: Just one comment. I think that probably does contain some people with real Borrelia burgdorferi infection. I think the sponsors data would support that even in culture-proven cases that not everybody sero converts. So that the serologic data cannot be used as a gold standard. And the fact that someone has erythema migrans and doesn't sero convert doesn't mean that that is not a Borrelia burgdorferi infection.

CHAIRPERSON FERRIERI: Exactly. And then the issue was raised earlier of early treatment which modifies serologic response. Any other comments on this? Is that sufficient, Dr. Elkins?

DR. ELKINS: Yes, thank you.

CHAIRPERSON FERRIERI: We will move on then to the question on the screen. We will not be voting on this question. This is amusing in a sense. Please comment on the

use of Lyme disease vaccine in persons over 70 years of age. We have heard the concerns here about whether the efficacy is as great as one would like in someone hovering in that 7th decade. But we have not seen data. Dr. Greenberg, on the greater than 70 years?

DR. GREENBERG: Do we know -- I don't know anything about the natural history of Lyme disease in the 70 and 80-year-old population. I mean, is this a big problem with my colleagues? I mean, I know there are elderly in the northeast, my mom being one of them. But she hasn't gotten Lyme disease recently.

CHAIRPERSON FERRIERI: Not yet. Who would like -- anyone on the panel who would like to speak first and then we can call upon anyone else.

DR. DATTWYLER: As a clinician in an endemic area, the elderly rarely come to us with Lyme disease. It happens rarely. The most common age groups are young.

CHAIRPERSON FERRIERI: Well, that is interesting. The activity and out of door activity of many people who are in their 8th decades is great in many parts of the country. So do you have any factual data on sero conversion in that age group in your endemic area?

DR. DATTWYLER: No, we have never studied that population. So unless they are just getting taken care of by other people. We don't see that many people in that age group. We have no data.

CHAIRPERSON FERRIERI: Thank you. Yes, from our sponsors. Dr. Sikand?

DR. SIKAND: Vijay Sikand. I respectfully disagree with the comment from Dr. Dattwyler. As a primary care physician, I see numerous patients in the elderly age group who develop Lyme disease. They get it paradomestically or they get it playing golf or they get it through whatever they do. And indeed a slide presented by Dr. Schoen earlier on the age incidence of Lyme disease I believe it was in Connecticut shows a significant number of patients during every decade right up to the age of 90 develop this infection on an annual basis.

CHAIRPERSON FERRIERI: And their presentations are not atypical.

DR. SIKAND: Indeed, they are more or less the same as much as can be said about Lyme disease, yes.

CHAIRPERSON FERRIERI: Thank you, Dr. Sikand.

DR. DATTWYLER: Guys like that are seeing them

and that is why we are not.

DR. DAUM: Why did you decide to exclude those people from the trial?

CHAIRPERSON FERRIERI: You didn't want people who might --

DR. SIKAND: I was an investigator and I followed the protocol which included individuals up to age 70.

CHAIRPERSON FERRIERI: I would imagine the concerns about natural death and cardiovascular complications and so on. The sponsors are nodding their heads at that, Bob. They wanted to stay away from anything that confound analyses of outcome.

DR. SIKAND: Clearly one was looking for a healthy population.

CHAIRPERSON FERRIERI: Yes, thank you.

DR. FLEMING: Just a -- Bob asked exactly the question that I would have asked as well. If we are sufficiently concerned about inclusiveness in our eligibility criteria and that is justified, then we ought to be equally concerned about extrapolating results from the trial when it is done. Either because in the beginning we didn't think it was as plausible that they would benefit or we thought they

might be at higher risk. So I am always troubled by the disconnect between having exclusiveness in my eligibility criteria and inclusivity in my labeling indication. What, in fact, is the substantive reason we didn't include them in the clinical trial that now shouldn't be as much a concern when we think of labeling?

CHAIRPERSON FERRIERI: Who would like to respond to that? Dr. Clements-Mann to this question?

DR. CLEMENTS-MANN: Well, I think that if one were looking at a population and the ability, as I think we are beginning to see, of being able to follow them long term, and also to select a population that would have the highest incidence of disease, then one might rationally conclude that that would be in the age range selected. I think that to get around this question, just as we do with other vaccine studies, one could do a bridging study to see how well people in the older age group respond. And within that age group, you are going to find that those people respond differently. Probably there will be the active elderly and then those who are frail or institutionalized who may not need the vaccine at all. So that it may need to be further stratified to see how they respond. But just in terms of finding an age through

that is active and that is out there exposed to ticks, probably the younger age group would be more likely to be exposed.

CHAIRPERSON FERRIERI: Tom? Dr. Fleming?

DR. FLEMING: Mary Lou, would that bridging study be one based on immunogenicity or would it actually be efficacy? There are some preliminary data, not the age above 70, but there are some preliminary data that we would be able to put forward that suggest that there is a trend toward lower GMTs as age increases. We notice that. I think Claire was noticing that in particular for the 61 to 70 age range. So if you do an immunogenicity study and that trend continues, how low do we tolerate the GMTs and say it is still protective?

CHAIRPERSON FERRIERI: Would you please respond, Mary Lou?

DR. CLEMENTS-MANN: I think there are a variety of ways. With other vaccines, it may take more doses, for instance, to achieve the same GMT. And there is also an interesting phenomenon that sometimes occurs at that upper age range and that those are perhaps more fit older people than the actual younger age range. So I think we just have to do the study to see how they do respond. Because it may be that

they respond equally as well as the 60 to 70-year-olds or they may need 4 doses instead of 3 doses.

CHAIRPERSON FERRIERI: If they were very active, it may imply they are in good health and their nutrition is good which may influence their immunologic response and so on. So all of these points are intimately related. Steve? Dr. Kohl?

DR. KOHL: And this dovetails with the necessity to define a protective level of antibody, which is one of the critical issues that has, I think, arisen from all of these discussions.

CHAIRPERSON FERRIERI: Yes. I am sure that CBER has heard us. We are saying it again and again. They and the sponsors absolutely need to be working hard on this issue. Dr. Breiman, did you have your hand up? Anyone else? Dr. Hall, and then we are going to move on to question 4.

DR. HALL: Is there any evidence that in the older patients that have Lyme disease that these are reinfections? Aside from just the GMT, that even early on that they have frequency greater of having antibodies previous to infection? There are no data?

CHAIRPERSON FERRIERI: The patients already

enrolled, Caroline, in 008, for example? Do we have any data to answer Dr. Hall's question? Pardon me? Yes, please. Caroline, could you repeat the question?

DR. HALL: I was wondering if the infection in the older age group, having lived through an endemic say area for 60 years, if those people who then you have mentioned that have clinical Lyme disease, if those are reinfections or any evidence that they have had previous infections? And if so and it is no different, then that gives us some data on some of these other concerns about reimmunizing and reinfecting.

DR. STEERE: I think that it has not been an endemic area for 60 years, or at least the endemic area has increased. The risk has increased. And consequently someone who has lived there for 10 years or 20 years may have as much risk as someone who has lived there for 60 years or about as much risk. I do not happen to know the age breakdown of the sero positive group at study entry.

CHAIRPERSON FERRIERI: Thank you. Dr. Finkelstein? Just one second. Dr. Parenti?

DR. PARENTI: Again, there were only about six positive people at baseline at study entry. I honestly don't recall their ages. Their titers were extremely low and again

they didn't boost on getting vaccine.

DR. HALL: Or outside of the vaccine study, just in those that are seen older -- older individuals who have Lyme disease, do we know what their antibody is early on or if they have had reinfection?

DR. PARENTI: I don't think that we have that kind of data that really break it down by age. On the other hand, what I think is that if you have had erythema migrans and are treated with antibiotic therapy, that sort of person can get infected again. Though I also think that if they do, there is usually what seems like an amnestic response and that the disease is milder. On the other hand, if Lyme disease has progressed so that you are months into the disease, that sort of person I believe from my experience has a protective immune response and they don't get infected again.

CHAIRPERSON FERRIERI: We will move on now. The next slide, please, question 4. In the efficacy trial, vaccinations were given just before the Borrelia burgdorferi transmission season at 0 to 1 month between January 15 and April 15. Then 12 months later between approximately February 15 and April 30. Should a similar seasonal vaccination schedule be recommended in the package insert? We will be

voting on this issue, but would appreciate anyone who would like to open discussion on this. Anyone who disputes that this vaccination schedule would not be recommended in the package insert based on the data we have, of course? Dr. Edwards?

DR. EDWARDS: I think we are being very careful about what we agree to based on the study that has been done. So I think in the same general way that we have been approaching the other issues, that we really need to go with how the study was designed in order to license the vaccine.

CHAIRPERSON FERRIERI: Other comments? Yes, Dr. Eickhoff?

DR. EICKHOFF: Well, ordinarily I would think the answer to that ought to be no. But Bob Daum has commented several times on the unusual repetivity with which the antibody levels decay, and I agree. It seems incredibly fast. So given the dynamics of the antibody response that we have seen, I don't see how we can do anything other but to recommend a seasonally based vaccination schedule.

CHAIRPERSON FERRIERI: Dr. Hall?

DR. HALL: I think that again in practicality it is a good idea to recommend it. The real companion

question is should it be implied if not recommended not to give it at other times. Because just like the influenza vaccine, we can say that it is best to give it at such and such a time, but if you don't give it then, give it when you can. Should that be the alternative here?

CHAIRPERSON FERRIERI: Any comments on this? Dr. Daum and then Dr. Kohl.

DR. DAUM: First, apologies to Dr. Eickhoff for being repetitive, but I did think it was an important point. So I needed to say it several times, I thought. But it comes up with this issue that two doses produced a relatively low GMT that had I think fairly minimal efficacy in the first season after the two dose regimen was completed. At least it wouldn't be enough for me as a patient to get excited about taking my chances with ticks or changing my behavior after receiving a two-dose regimen. I don't know whether the seasonality has anything to do with it or not. The point is that someone is going to start their immunization schedule prior to tick season number one, get the two-dose regimen, but really not have that good high efficacy until the third dose comes prior to tick season number two. And so I think that there is going to have to be a lot of patient education here

that the two-dose regimen you have just received prior to the warm weather doesn't allow you to go play in the woods willy nilly and expect efficacy against this disease. And it is not going to be until next year when you get that third dose under this schedule that the real high or the relatively high efficacy kicks in. And I think that is going to turn out to be an important issue in the uptake and how people think about this vaccine. So I am not sure it is the seasonal vaccination schedule, but it sure looks like that third dose looked pretty important to me.

CHAIRPERSON FERRIERI: Well, it is important and the issue of compliance and memory of coming back for your injection. So if you are privileged and you are on the Internet, then your healthcare system may send out messages when your next shot is due. But you almost need to be within a care system that is sending out reminders, memos, post-cards, or e-mail to you. Dr. Fleming?

DR. FLEMING: I read the question as should a similar seasonal vaccination schedule be recommended. If it is intended to say recommended and not mandated, I can't think that we could say anything -- I could say anything but yes to recommending it. When we look at the pattern of GMT levels

and we see a tenfold higher GMT level in the second year and we see much higher efficacy, it certainly is suggestive that these higher GMT levels are potentially predictive of level of protection. And we see that with the schedule as it was given, when you get it at 1,000 and it is roughly the seasonal exposure of when you are still about 600 or 700 and it gets down to 100, it would suggest to me very strongly that I would recommend -- I would exactly agree with Bob. That first year, you are still at risk. But it certainly seems to be recommended that you get it at a time frame that you are going to have the higher level during that first year. So I would -- if the word is recommended rather than mandated, I would strongly agree.

CHAIRPERSON FERRIERI: Again, we keep hearing the issue of levels of antibody. Dr. Coyle?

DR. COYLE: Well, I might almost argue that you have to give it this way. That you might be in trouble or be misleading if you didn't give it this way. And the difficulty is the peculiar seasonality of the infection, the risk of getting infected, and then that the antibody levels seem to be so critical. You might be in trouble if you didn't follow this sort of schedule.

CHAIRPERSON FERRIERI: Other comments? Everyone wants to contribute. We will go over to this side of the table and then I will come back. Harry and then a few others.

DR. GREENBERG: I would just simply say that as best I know, there is no other vaccine that takes a year to develop real efficacy, and I would recommend to the manufacturers that this is not at all optimal. You are asking somebody to buy into vaccination for a whole year before they get benefit, which is not ideal. I know you are doing trials to figure out a better way of doing it.

CHAIRPERSON FERRIERI: Sponsors, you can respond. Please give your name again.

DR. KRAUSSE: David Krausse, SmithKline Beecham. There are other vaccines which take 7 months to develop gold standard immunity. We fully agree with your statement that other schedules are to be desired.

CHAIRPERSON FERRIERI: Thank you. Dr. Finkelstein?

DR. FINKELSTEIN: I just wanted to ask the sponsor, was it essential to wait that year for the third boost of vaccine? Why does it have to be 0, 1, and then not

until 12? Is that essential?

CHAIRPERSON FERRIERI: Dr. Parenti?

DR. PARENTI: The original study design was thinking that we had the two-dose vaccine and the third dose would be a booster dose. So that might be it.

DR. FINKELSTEIN: So there was no reason why you couldn't probably give that third dose after two months or something? And maybe if you got the efficacy immediately, you could protect that first year as well, is that right?

DR. PARENTI: Yes. If I could, I will show some GMTs after three doses.

CHAIRPERSON FERRIERI: I don't think we have the need for it nor the time right now. Dr. Karzon?

DR. KARZON: I think this schedule is astute. It is good immunologically. It is good ecologically and it is sound. It gives 50 percent effectiveness the first year and 80 the next year and hits the peak at the right time. I don't see any downside except it is a little unusual, but so is the disease.

CHAIRPERSON FERRIERI: Retort here? Dr. Finkelstein?

DR. FINKELSTEIN: I would just follow up that

it might be -- I mean, while this is the only trial on which one could make recommendations because nothing else has been presented to us, it might be useful for the sponsor to attempt to do a different schedule and improve on this.

CHAIRPERSON FERRIERI: They are. They are working on it. They have other projects ongoing, Dianna. Dr. Kohl?

DR. KOHL: What I would like to ask the Lyme experts is in other parts of the country -- not the hyperendemic areas but other parts of the country which don't have as clearcut seasonality as the northeast, for instance, is there a slightly different or very different maybe epidemiology in terms of seasonality of Lyme as there is for enterovirus, for instance, or other viral diseases?

DR. STEERE: Yes. My understanding is that the disease is less seasonal in California.

CHAIRPERSON FERRIERI: If I could just bring to your attention the alternate schedules that are being examined. 0, 1, and 6 months versus 0, 1, and 12. Other alternatives -- this is the one I particularly like and I hope the data support my affinity for it -- 0, 1, 2, and 12 months versus 0, 1, and 12 months. So we have a lot to look forward

to. Dr. Coyle?

DR. COYLE: Don't you think it is an important point that if this winds up being approved by the FDA that it be clear that people be actively discouraged to use experimental protocols until you have something documented? I mean, I don't know if you can say mandated, but you might really be in trouble if you switched the schedule. And granted, it is far from optimal. That one year of not being protected 50 percent is poor frankly. But how could you have people experimenting with well let me do it once a month for three months. We can't extrapolate. CHAIRPERSON FERRIERI: Agree. Dr. Snider?

DR. SNIDER: Well, let me say that I understand why based on the data we have in front of us we might agree with the recommendation in the package insert should be exactly the way the study was done. However, when you put the realities in front of another committee, such as the advisory committee on immunization practices with which I have some familiarity, or even you put the realities in front of the clinician, the patient who presents for the first time on April 16 for the first dose, or the patient in California who presents any time of year outside the range given there, then

I think some individual judgments are going to have to be made. Outside the northern endemic areas -- what about the southern United States? What about the further south you get? What about the seasonality there? It seems to me that a recommendation based on the way this particular study 008 was designed is reasonable to put in the package insert. But I would be very reticent to put in much stronger language to keep people from using the vaccine in other circumstances which on their clinical judgment may offer great benefits to the patients and offer little risk. I realize there is not a large data base, but often we have to extrapolate.

CHAIRPERSON FERRIERI: The word recommended seems to get lots of nods of affirmation at the table. Dr. Broome and then Dr. Luft.

DR. BROOME: I think this is a great example of the problems between efficacy studies and effectiveness studies. I think the schedule was clearly designed to optimize the chances of showing efficacy, not to help a clinician have a reasonable schedule option. I think the implications for us and for the ACIP is that us, FDA and advisory committee, need to see a really thoughtful analysis of what can be learned from the efficacy study about

surrogates. Because I would assume that is how we are going to move from where we are to where we would like to be. And so far, I think there is a lot more that could be mined from the efficacy study, although I think it is going to be limited by the way it was designed.

CHAIRPERSON FERRIERI: Thank you. Dr. Luft?

DR. LUFT: I just -- I don't know whether I misunderstood it, but I think the regimen of 0, 1, and 12 was really -- it sounded like it was decided upon post hoc. You know that the 12-month immunization was added on. So to kind of think that that is an optimal immunization regimen, perhaps they saw that the titers were dropping or whatever. I don't know. But it would be apparent that this is not the optimal way to immunize. But on the other hand, I think that as Dr. Daum has mentioned over and over, the kinetics or the dissipation of this antibody response is really quite remarkable as well as the boosting effect. And we really don't have -- or I haven't seen much data as to what the kinetics are that are necessary in order to be able to optimize antibody production. So for all I know, maybe you need a 12-month period of time when you need that boost in order to be able to get an optimal antibody response, and I

think that this is really the subject of further studies and we should make that as a recommendation perhaps in number 5 -- question 5, I think.

CHAIRPERSON FERRIERI: We have already made that recommendation in number one, I think. Sponsors, please?

DR. KRAUSSE: Yes, David Krausse. The study was prospectively designed to be a two-year study with a 0, 1, 12 schedule. So we should put to bed the idea that this was retrospective. That is why we had 95 percent of the subjects come back for the month 12 visit. If we knew that the efficacy were to be 50 percent after two doses in the first year, obviously that would not have been the schedule that we had chosen. But we tried to balance convenience to the vaccinee with the optimal efficacy based on Phase II data and on animal data.

CHAIRPERSON FERRIERI: Thank you, Dr. Krausse. I think we are ready to cut bait here. We will start voting. Dr. Dattwyler, the voting if we can with the precise wording that is on the screen.

DR. DATTWYLER: I agree with that with the idea that further studies need to be done, which we will discuss, I guess, next.

CHAIRPERSON FERRIERI: Thank you. Dr. Coyle?

DR. COYLE: Yes, I agree. And I might almost add that at least in seasonal areas that they be discouraged from using a different formula until there is better data.

CHAIRPERSON FERRIERI: Thank you. Dr. Luft?

DR. LUFT: Yes, I concur.

CHAIRPERSON FERRIERI: Dr. Broome?

DR. BROOME: Yes. I think, though, that we have to be clear that at least for the first season it is a strong recommendation because of the concern that efficacy would be substantially less if you don't follow it.

DR. BREIMAN: Yes.

CHAIRPERSON FERRIERI: Do I understand you correctly then, Claire, that you are recommending strongly that injections 1 and 2 be given as stated?

DR. BROOME: Until we have further data.

CHAIRPERSON FERRIERI: Dr. Eickhoff?

DR. EICKHOFF: Yes.

DR. DAUM: Dr. Fleming?

DR. FLEMING: Yes.

CHAIRPERSON FERRIERI: Dr. Kohl?

DR. KOHL: Yes. But I am still concerned about

geographic specific recommendations.

CHAIRPERSON FERRIERI: Thank you. That will be noted. Dr. Karzon?

DR. KARZON: Yes. But obviously the ecology has to be followed. And if the facts are that the epidemicity is different in Florida than it is in northern Minnesota, which I wouldn't doubt, that should be discerned and put in here. I think this has to be accompanied by the fact that this trial was conducted under these circumstances and that the goal is to maximize the level of antibody at the time of the challenge. And that regional decisions will have to be made to modify this. I want to add one other thing. There is a lot of experience with childhood non-replicating vaccines that a priming dose of 0 and one month or 0 and 2 months is a common pattern and then a longer interval for a booster. If you look at the efficacy of boosters prior to say 3 months, you get a poor response. You get an additive effect and not a booster response. But if you wait a minimum of about six months, with a variety of non-replicating antigens you get a good boost. The 12 months is simply a prolongation of the six months so it works fine. But this has to be verified experimentally. I think some intermediate experiments are

going to have to be done in children or where the epidemicity is such that it is perennial to see what minimal time has to pass before you can give a third booster dose.

CHAIRPERSON FERRIERI: Thank you. Mrs. Cole?

MS. COLE: Yes.

CHAIRPERSON FERRIERI: Dr. Daum?

DR. DAUM: Yes. I like very much the point of Dr. Karzon that pointed out that the reason for the recommendation was that the study that documented the efficacy was performed in this way and would even go a step further and say that other regimens at this moment have not been evaluated and that that is the reason for the recommendation.

CHAIRPERSON FERRIERI: Dr. Finkelstein?

DR. FINKELSTEIN: Yes.

CHAIRPERSON FERRIERI: Dr. Clements-Mann?

DR. CLEMENTS-MANN: Yes, and hopefully this recommendation will actually spurn the company to identify the level of antibody and do the bridging studies so that we can get a vaccine that will achieve the 80 percent effective level in the first year.

CHAIRPERSON FERRIERI: Dr. Greenberg?

DR. GREENBERG: Yes.

CHAIRPERSON FERRIERI: Dr. Hall?

DR. HALL: Yes, and I am still concerned about the wording and how this will be set in that there will be no -- or there will be a lack of guidelines for those instances which may be the majority of instances in which the patient does not present at exactly the right time or where there is geographic variation of risk.

CHAIRPERSON FERRIERI: Do you consider that clinical judgment could be inserted here in terms of best judgment?

DR. HALL: Well, there will be some guidelines needed.

CHAIRPERSON FERRIERI: Thank you.

DR. HALL: This would be optimal given the situation of this particular study. But what do we have to offer the rest of the world?

CHAIRPERSON FERRIERI: Thank you. Dr. Snider?

DR. SNIDER: I would say yes. I would agree with a lot of the comments that David Karzon made. And I guess the caveat I would also have in addition to the clinical judgment is that this would apply where Lyme disease is seasonal. If it is not seasonal, I think you would adhere to

the intervals because that is what we know. But I don't see any point in adhering to a seasonal vaccination schedule if Lyme disease is not seasonal in that particular area.

CHAIRPERSON FERRIERI: Okay. Dr. Huang?

DR. HUANG: I concur with all the previous comments.

CHAIRPERSON FERRIERI: Dr. Edwards?

DR. EDWARDS: Yes.

CHAIRPERSON FERRIERI: Dr. Poland?

DR. POLAND: Yes.

CHAIRPERSON FERRIERI: And for the record, my vote is yes as well. We will move on to the next slide and the last question.

DR. ELKINS: Dr. Ferrieri?

CHAIRPERSON FERRIERI: Yes.

DR. ELKINS: If I could offer a point of clarification. I sense frustration on the part of the committee and we share that. I know the sponsor does concerning studies on the serologic correlate. We happen to have here an unusual situation in which the efficacy data became available well in advance of the complete analysis of the serological correlate. And given the nature of the

efficacy data, we thought we would be remiss to not bring it forward as it stands. But I assure you that those data will be forthcoming and you will have them to look forward to in the future I believe.

CHAIRPERSON FERRIERI: Thank you, Dr. Elkins. The question is are there any additional studies that should be performed by the sponsor. We have already proposed a couple of them. One of them that dealt with chronic joint disease patients and patients with other arthritides and gave more details of our requirements than you might ever want to hear. And we have also proposed the long-term duration studies for booster patients who are enrolled in some of these other studies as well as new studies that might be proposed for boosters. And then thirdly what we have just heard that because of the ephemeral nature of antibody responses in many patients that we are eager to see this type of antibody data and correlation as well and long-term follow-up on this in terms of immune protection. So I will open this up for responses to the other issues that Dr. Elkins mentioned to us, and this included the rare adverse events studies and secondly studies in children. I would like the committee to respond in particular to how their interpretation of the data they have

heard today in general would impact any guidelines that we would recommend for the conduct of these studies in children under the age of 15. So I would like to get some responses from you. I know you may be tired and the hour is late, but we are almost at the finish point. Dr. Finkelstein?

DR. FINKELSTEIN: I think in your list that I don't think I heard the elderly age group.

CHAIRPERSON FERRIERI: Yes. That was among the ones that we have proposed.

DR. FINKELSTEIN: And also other schedules.

CHAIRPERSON FERRIERI: Correct. Any other responses to the issues we haven't discussed yet? We have discussed quite a bit on the other. Yes, Dr. Clements-Mann?

DR. CLEMENTS-MANN: Just out of curiosity, what schedule were the placebo recipients given the vaccine?

CHAIRPERSON FERRIERI: Dr. Parenti?

DR. PARENTI: I am sorry, I answered too fast. The placebo subjects were subsequently transferred into several other studies. Some looked at four doses of 0, 1, 2 versus 0, 1, 12. Some got 0, 1, 12.

CHAIRPERSON FERRIERI: Let us tackle maybe the issue of rare adverse events and how you would like to proceed

to gather more data. Dr. Edwards?

DR. EDWARDS: Is there any data regarding the antibody levels to these proteins in children that have arthritis? Are the patterns that are seen in pediatric cases different than those in adults?

DR. STEERE: You mean in the natural history of the disease?

DR. EDWARDS: Correct.

DR. STEERE: Arthritis may be milder in very young children of 2, 3, or 4. But once you get past that point, it seems quite similar to what you see in adults, both clinically and serologically.

CHAIRPERSON FERRIERI: Yes, Dr. Breiman?

DR. BREIMAN: I think we need something on the order of what we had with the large link data base to follow these patients. The problem with at least my understanding of the current formulation of the vaccine safety data link or the large link data base is that it is mostly on the West Coast, or I think it is entirely on the West Coast. But it seems to me that having some kind of registry that keeps records of immunization status and then both adverse short-term as well as long-term events is something that we need. We need that

not only for this vaccine actually, but this is one situation where it would be very helpful. How to bring that about and who would be responsible for implementing such a registry is another question, I guess. But it seems to me that we are not going to get these questions answered in a pre-licensure situation and it is going to fall now on the next phase.

CHAIRPERSON FERRIERI: True. Dr. Luft?

DR. LUFT: Well one I think very large issue, and I am not sure it is within the purview of this group, is that the sero diagnosis for Lyme disease in the vaccinated patient population has become extremely difficult and very expensive as a result of this vaccine. What is happening is that all current ELISA's will no longer be useful and that we will have to use Western blot, which is a very costly diagnostic test for the primary diagnosis of patients. And I think that there has to be some work done for the development of new diagnostic testing as well as new diagnostic criteria for this particular patient population. It is going to become a very cumbersome and expensive venture.

CHAIRPERSON FERRIERI: We need a little microchip and the ability to do PCR by automation. And that is not an idle dream. Dr. Broome? That will come.

DR. BROOME: Just a couple more comments on the safety issue vis-a-vis chronic arthritis or the chronic arthritis population. I think it would be very useful to do some realistic sample size estimates either looking at what is our comfort level with data from the efficacy study in terms of projected frequencies of DR susceptibles, projected frequencies of annual progression to severe disease, and whether or not you would detect an increased frequency of that within the sample size studied. I think those calculations could also be helpful in saying whether or not it is feasible to do a prospective study within the groups excluded from the trial. I just have no idea whether that is -- you know, what order of magnitude are we talking about for sample size and how feasible such a study would be given that you were dealing -- if you were dealing with a licensed product. If it is not either logistically or ethically feasible to do it in a prospective controlled fashion, then I think rather than what Rob is calling a registry, I think what we really mean is a defined data base which identifies both vaccine history and disease outcome history in a substantial population. I think what we are saying is that passive surveillance is not going to answer this question in terms of the complexity of deciding

whether or not vaccination is or is not associated with chronic arthritic.

CHAIRPERSON FERRIERI: Thank you, Claire. There are six of us on the committee who are pediatricians, so I would like to really squeeze you on your ideas on the vaccination studies in children, whether they are already initiated, the direction they will go, what types of guidelines would you impose on these studies. Dr. Kohl?

DR. KOHL: Maybe I am missing the boat, but I think once we get reasonable antibody correlates, we need to define in children what optimal schedules are that will give us high and sustained levels of those antibodies as best as possible. The company is starting to do that, and I would urge them to continue to do that.

CHAIRPERSON FERRIERI: And regarding safety issues? Anyone? Dr. Edwards?

DR. EDWARDS: Well, I think it would have been nice to have looked at the data much more completely than it was simply presented. So I think that that might be something that we could do. If we could see the data and go over it more carefully and get some idea what the reaction rates were, whether arthralgia was seen and also some of the issues

regarding other safety parameters and the numbers of patients. I think it would be helpful to be able to look at that data much more completely.

CHAIRPERSON FERRIERI: Thank you. Other points on this specific issue? Dr. Daum?

DR. DAUM: If this going to be used for children who are receiving this vaccine at a time when they are receiving other routinely recommended diseases, there may be some vaccine antigen interference issues that need to be addressed as well and that needs to be thought through carefully.

CHAIRPERSON FERRIERI: Very excellent point. Before I call on Dr. Huang, do any of the other pediatricians want to comment on this theme?

DR. HALL: Yes.

CHAIRPERSON FERRIERI: Yes, Dr. Hall?

DR. HALL: Just mentioning the same thing. Not only the combination of vaccines being given with other vaccines. But in the schedules that are to be looked at to consider what the current vaccination schedule is and whether that can fit in in any way with it. That is important in compliance.

CHAIRPERSON FERRIERI: Agreed. Any comments on this issue? Dr. Karzon, the pediatric trials, safety, et cetera?

DR. KARZON: Well, we have big experience in putting new vaccines into children. We usually do it in adults and gain some appreciation of the correlates of immunity so that you have some endpoints. And then you start in children 5 and above and then you get down to the younger ages. On several grounds, little children are going to be different in their reactivity and their immunogenicity, so you work downwards in terms of safety and discovering an optimal schedule. But as I said, it is classical to end up with two doses and then an interval and then another dose. Then the last thing you have to do, as has been mentioned, is correlate it with other immunogens given in the children's period.

CHAIRPERSON FERRIERI: Dr. Kohl?

DR. KOHL: This one may be a little bit different because the epidemiology may be different. And I guess again I will ask Allen and others in the audience. We probably don't see much Lyme disease under the age of a year, probably not even under the age of a year-and-a-half. And this may not be a vaccine that we want to start in the infant.

This may be a vaccine we want to start in a one or two-year-old, which would be quite a departure from our routine immunization schedules.

CHAIRPERSON FERRIERI: Thank you. Dr. Huang and then Dr. Snider.

DR. HUANG: Well, I am certainly not talking from the perspective of a pediatrician, but in listening to the comments here, I wanted to say that this has been an extraordinarily difficult decision for many of us, and I think the comments have been very carefully thought out. But if we step back and really look at this particular vaccine, it is something that has an unusual three-shot deal for one season of protection, and it may end up having some long-term sequelae that we now have no ideas about. But because of both humoral and T cell involvement, there is something to worry about. So in looking at this and for what we are getting out of this, I would say that for those who are in the process of developing this vaccine and getting it licensed, not to sell it immediately tomorrow and push it as hard as you can for all the money you can get. But that it may be worthwhile getting a little bit more data and getting better timing and scheduling of the dosages and the amounts and just waiting a

little bit longer may not hurt. I know that we all voted yes on many of these issues and I know that I did it because I know that there is tremendous public interest and pressure on this. And that, yes, we do have a vaccine that I am comfortable with, but it is not something that I would push tomorrow.

CHAIRPERSON FERRIERI: Dr. Snider?

DR. SNIDER: I was going to make the same comment that Dr. Kohl made about perhaps we don't need to do this in young children. Often we are concerned about the issue of dealing with premature infants, and I don't think in this particular case that there would be an issue there. But it occurs to me that there is another group and that is the pregnant women that I hadn't heard whether they were included in the trial or not and whether we had any information. I didn't see a specific exclusion on the list I saw, but maybe I was only looking at the short list and not the long list.

CHAIRPERSON FERRIERI: There were cautions. Dr. Krausse, could you respond to that?

DR. KRAUSSE: Pregnant women were excluded from the trial. And also in response to Dr. Huang, I think that we agree with you that safety studies are necessary to do in

children. I think we have proceeded very cautiously. On the other hand, I will say that many of the subjects in the trial, and probably Dr. Sikand can speak to it better than I, were very, very anxious for their children to participate in trials. So we have a long list of children who are waiting to participate.

CHAIRPERSON FERRIERI: Thank you. Dr. Daum?

DR. DAUM: I guess to return to something I mentioned before. I would like to see some OspA gene monitoring as this program goes forward. And particularly I guess the points to consider would be twofold. One would be from people who are vaccine failures, whether the OspA gene in that strain has mutated. If they are failure isolates, it might be interesting to look at them. And then secondly -- so I guess I would make an extra effort to get failure isolates. I guess that is the first thing I am saying. And then the second thing is that it might be worthwhile maybe on an annual basis to take a subset of strains and just have a look and make sure that those regions which strike me as very, very conserved remain that way under antibody pressure.

CHAIRPERSON FERRIERI: Thank you. The sponsors would like to respond to that. Dr. Lobet?

DR. LOBET: Yes, we have already sequenced the OspA gene from 80 different strains that were collected during the efficacy trial. 20 of these strains were coming from the vaccinees or the breakthrough cases. So those are basically all the strains that are available. And we see basically no difference between those strains and any of the other known strains that were known previously -- those that I mentioned, N4297 and so on. You have basically variations in three positions. For each of these three positions in most cases there are just two possible amino acids. You have actually five different categories and those correspond to different combinations of those variations.

DR. DAUM: That is wonderfully reassuring. And now that you have proposed to give the vaccine to millions of people, you may see something different. So all I am asking for is that it be monitored and thought about.

CHAIRPERSON FERRIERI: Dr. Clements-Mann?

DR. CLEMENTS-MANN: I realize this is probably obvious, but it would seem that perhaps a better adjuvant might help make the vaccine more immunogenic and reduce the number of doses.

CHAIRPERSON FERRIERI: Would sponsors like to

respond to that? Well, it is an item that requires further examination surely. We are straying into highly secret territories perhaps. There are many other people who had their hands up. Those of you who haven't had a chance to say much today, any of you here yet?

DR. SNIDER: I wanted to follow up on the pregnant women issue because it comes back then to who this is going to be recommended for. Because if women of childbearing age or women who are pregnant or planning to become pregnant or who may become pregnant are also on the exclusion category, that could be a fairly large number of people from whom the vaccine will be held. So it is not a trivial issue. I am sorry I didn't get it in earlier.

CHAIRPERSON FERRIERI: That is all right. In the proposed package insert, I thought this issue was addressed. Would sponsors like to clarify that point? I don't remember it verbatim. But there were several lines written in to cover all possibilities, although as they have said in the trials they were excluded. Dr. Krausse?

DR. KRAUSSE: Well, I am not aware of too many vaccine studies that the first go around that pregnant women are vaccinated. Of course, it is a recombinant protein and

not an attenuated bacterial or particle. The FDA has already asked us to perform one additional preclinical study, which we have agreed to do. That is it.

CHAIRPERSON FERRIERI: In the -- if I might read from this, I don't know whether it is still valid or will be next week. But it indicates some caution on teratogenic effects in pregnancy category C. It is not known whether LYMErix can cause fetal harm when administered to pregnant women or can affect reproduction capacity. It should be given to a pregnant woman only if clearly needed. Comments on nursing mothers and caution when administered to a nursing women. So the package insert does not exclude its use and indicates if clearly needed. So it becomes a judgment call. Does FDA wish to comment further on this and how the agency would -- what the party line would be from the agency on this given all that we know about this vaccine?

DR. SNIDER: I was just concerned because we had, I think, gone on record as being very conservative in terms of how we were recommending this in the context of how it was used in the trial.

CHAIRPERSON FERRIERI: Right. Dr. Elkins or one of you from the agency wish to respond?

DR. KRAUSSE: Well, actually I think I will let Dr. Hardegree.

DR. HARDEGREE: I think that it is important to recognize that the package enclosure document that you have in front of you is one that has been proposed. We are taking all consideration of comments that people are making here and any additional data we have. But we do share your concerns about this recognizing that it is likely to be used and there is no data. I think we have to state when we don't have information.

CHAIRPERSON FERRIERI: Further comments on this very important issue? Dr. Greenberg?

DR. GREENBERG: My comment is not related to pregnancy.

CHAIRPERSON FERRIERI: Any further issues on pregnancy? Dr. Luft? And then we will come back to you.

DR. LUFT: I think it is important to realize that this vaccine has a built in adjuvant in it. I mean, it is a lipoprotein and I am not sure how many vaccines are out there that are lipoprotein that has a variety of immunogenic activity in itself and how that might affect either the fetus or the reproductive status of the individual is really

unknown. So I would be very -- I would approach that whole issue as to vaccinating someone with a lipoprotein with real caution. Just because we don't have any data in that regard.

CHAIRPERSON FERRIERI: I would just reemphasize what Dr. Krausse says that this was not some intentional -- well, you don't have to include pregnant women and children in all vaccine trials obviously. Dr. Greenberg?

DR. GREENBERG: I just want to reemphasize what Dr. Broome said. I have enough concern about the safety here that simply passive surveillance will not be adequate and that I really want some form of active system built in that is reasonably enduring that can follow vaccinees over a period of time and look for associations with arthritic complications.

CHAIRPERSON FERRIERI: Other important points? Dr. Fleming?

DR. FLEMING: I am delighted to hear that. I wanted to basically reiterate the same. Both Rob and Claire some time ago had raised this issue that the long-term follow-up here beyond this 12 to 20-month framework for both efficacy and safety is really key and what is being suggested here is more than a passive surveillance approach. Rob, I think, used the concepts of large link data bases or registries, and

Claire had said it certainly should be active. And I think what she was saying, or at least in my own words, in addition to an active surveillance of these individuals who are vaccinated, it will really be important to try to gather some reference information or other sources of data that would allow us to get better clues about levels of risk of significant disease-related events as well as vaccine-related events. We need the disease-related events -- we need to know natural history basically to be able to put into proper context what we are going to be seeing with this active surveillance so that we can see whether or not we are increasing beyond natural levels of risk, or better yet decreasing, which is additional evidence of efficacy beyond just preventing EM. So I would endorse what I now have heard three other folks saying, that this level of follow-up should be active and it should make an attempt to include additional sources of information to put into context what should have been seen in natural history in the absence of the vaccine.

CHAIRPERSON FERRIERI: Any other final points before I summarize? Dr. Poland?

DR. POLAND: Again, I will raise the point that I think one could prospectively and efficiently enroll people

known to be DR4 and hyperimmunize them in an attempt to try to rapidly get at the idea of whether with repeated doses they might suffer some rheumatic effect. This could also be done in transgenic mice with human DR4. And the other point that I would make is that I think vaccine failures should be HLA typed. There may be some valuable information there. And lastly, there are more than just DR associations with rheumatoid arthritis. There are also DQ associations and we haven't heard anything about DQ. And it might be important and interesting to look not only at DR but DQ.

CHAIRPERSON FERRIERI: Thank you. On behalf of the committee members, I want to thank the sponsors for the presentations. I think that there is a consensus of the committee that these are very carefully carried out studies. This was obviously a very controversial subject and we have exhausted many, many aspects of it. A great deal of caution was iterated by most of us and the endorsement regarding safety was with considerable ambivalence, but in general there was consensus.

The major issues that confront us and that I think will be followed through by CBER as well in collaboration with the sponsor include the critical issues

indicated on active surveillance, the adequacy of long-term and the need for long-term follow-up, the optimization of duration of protection, a better understanding of what the best schedules would be to lead to the most immunologic protection, and very importantly certainly a better understanding of what the immunity to this organism is. We have made suggestions on examining older age groups, pursuing the studies in children by optimizing schedules and a better understanding of antibody data as it would apply to them. A great concern about safety issues as it applies to the pediatric studies, and the possibility of these rare events, at least acknowledged as rare in the moment in patients who may have a particular susceptibility or have a genetic profile such as their DR allelic status, and a better understanding of vaccine combinations and any conflicts that would proceed from addition of this to a very complex and burdensome immunization schedule already in children. There are other issues that I won't pursue that you have heard us present. We look forward to discussing this issue with you again hopefully at a later date. Thank you all.

(Whereupon, at 6:15 p.m., the meeting was concluded.)

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