UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

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MEETING

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WEDNESDAY,

JANUARY 31, 2001

The meeting was held at 9:00 a.m. in the Versailles Rooms I, II, and III of the Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, DR. ROBERT DAUM, Acting Chair, presiding.

PRESENT:

MARY K. ESTES Ph.D.
STEVE KOHL, M.D.
KWANG SIK KIM, M.D.
ALICE S. HUANG, Ph.D.
ROBERT S. DAUM, M.D.
DIXIE E. SNIDER JR., MDD., M.P.H.
DAVID STEPHENS, M.D.
DIANE E. GRIFFIN, M.D., Ph.D.
AUDREY F,, MANLEY, M.D., M.P.H.
PAMELA DIAZ, M.D.
BARBARA LOE FISHER
JUDITH D. GOLDBERG, D., S.c.D
WALTER L. FAGGET, M.D.

NANCY CHERRY
Executive Secretary
DENISE ROYSTER
COMMITTEE MANAGEMENT SPECIALIST

CONSULTANTS PRESENT:

DR. PATRICIA FERRIERI
DR. MARTIN MYERS
DR. JUDY GOLDBERG
DR. MICHAEL O'FALLEN
DR. JEFFREY DAVIS
DR. PAT COYLE
DR. BEN LUFT
DR. WAYNE RAY
DR. RAY DATTWYLER
DR. ROBERT BALL
DR. SUE ELLENBERG

FDA REPRESENTATIVES PRESENT:

DR. KAREN MIDTHUN
DR. PATRICIA ROHAN

MANUFACTURER REPRESENTATIVES:

DR. CLARE KAHN - SmithKline Beecham
DR. YVES LOBET - SmithKline Beecham
DR. FRANCOISE MEURICE - SmithKline Beecham
DR. BERNARD HOET - SmithKline Beecham
DR. RICHARD PLATT - SmithKline Beecham
DR. DAVID WHEADON - SmithKline Beecham

VAERS REPRESENTATIVE:

DR. ROBERT BALL

PUBLIC PRESENT:

DR. SIDNEY M. WOLFE
KAREN FORSCHNER
STEPHEN SHELLER
JENNY MARRA
KAY LYON
EMILY S. BEIGEL
LYNN LANE
JOHN HARDY
PAT SMITH
LORI GELBART
LINDA SCHARF-LURIE
TERRY ELIAS
DAVID WELD
PAT EASTON

PUBLIC PRESENT: (Cont.)

DR. KENNETH DARDICK
KAREN BURKE

I-N-D-E-X

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

(9:05 a.m.)

CHAIR DAUM: We are gathered, or about to be gathered, I guess, in a slightly unusual configuration today, in that some of our FDA colleagues are going to be joining us at the meeting table, if they haven't already.

I would like to begin in our usual way of asking the committee members to introduce themselves. And with all due respect from criticism I received yesterday, we will start with Dixie this morning, if you wouldn't mind.

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

DR. STEPHENS: David Stephens, Emory University, Atlanta, Georgia.

DR. KIM: Kwang Sik Kim, Johns Hopkins.

DR. GRIFFIN: Diane Griffin, Johns Hopkins, in Baltimore.

DR. KOHL: Steve Kohl, Oregon Health Science University.

DR. MANLEY: Audrey Manley, Spellman College, Atlanta, Georgia.

DR. DIAZ: Pamela Diaz, Chicago Department of Public Health.

MS. FISHER: Barbara Loe Fisher, National Vaccine Information Center.

DR. FAGGET: Walt Fagget, private practice, pediatrics, National Medical Association.

DR. ESTES: Mary Estes, Baylor College of Medicine, Houston, Texas.

DR. FERRIERI: Patricia Ferrieri, University of Minnesota Medical School, Minneapolis.

DR. MYERS: Martin Myers, National Vaccine Program Office.

DR. GOLDBERG: Judith Goldberg, New York University School of Medicine.

DR. O'FALLEN: Michael O'Fallen, Mayo Clinic.

DR. DAVIS: Jeff Davis, Wisconsin Division of Public Health.

DR. COYLE: Pat Coyle, SUNY, Stonybrook.

DR. LUFT: Benjamin Luft, SUNY, Stonybrook.

DR. RAY: Wayne Ray, Vanderbilt University, Nashville, Tennessee.

CHAIR DAUM: Thank you very much. I'm Robert Daum from the University of Chicago.

I would like to turn the floor over now to Nancy Cherry, who will read the conflict of interest statement.

MS. CHERRY: Before I do that I would like to add a welcome to Dr. Daum, welcome to you, and make my usual announcement which is, for any of you that are parked in the public parking area across the street, please be vigilant, don't

let your meter run out of quarters, because those lots are checked very carefully.

I would also like to just make a note for the record that the arrangements for today's meeting were made by Denise Royster, who is the Committee Management Specialist. And you will find her at the front desk, assisted by Rosanna Harvey, and Sheila Langford. And I know Sheila is in the room. Rosanna is in the room, I guess Denise is probably at the desk right now.

Now, for the conflict of interest statement.

The following announcement addresses conflict of interest issues associated with the meeting of the Vaccines and Related Biological Products Advisory Committee of January 31, 2001, for the discussion regarding a vaccine for the prevention of lyme disease.

To determine if any conflicts of interest existed, the Agency reviewed the submitted agenda, and all financial interests reported by the meeting participants.

As a result of this review, the following disclosures are made related to the discussions regarding lyme disease. Dr. Alice Huang has recused herself from this discussion; Dr. Jeffrey Davis has been granted a waiver in accordance with 18USC208(b)(3), which permits him to participate fully on the discussions on lyme disease.

Drs. Dattwyler, Daum, Ferrieri, Goldberg, Griffin, Katz, Kohl, Luft and Snider have associations with firms that

could be, or appear to be, affected by the committee discussions.

However, in accordance with 18USC208 and section 2635502, of the Standards of Conduct, it has been determined that none of these associations is sufficient to warrant the need for a waiver, or for a written appearance determination.

In the event that the discussions involve specific products or firms not on the agenda, and for which FDA's participants have a financial interest, the participants are reminded of the need to exclude themselves from the discussions. Their recusals will be noted for the public record.

With respect to all other meeting participants we ask, in the interest of fairness, that you state your name, and affiliation, and any current or previous financial involvement with any firm whose products you wish to comment on.

CHAIR DAUM: Thank you very much, Nancy. Before we proceed to the open session, and the topic of the day, I would like to call on Dr. Bart Classen, who wishes to address the committee in open public hearing for five minutes.

Dr. Classen?

DR. CLASSEN: Thank you. I have been here before the Committee on the past to present some data on a large prospective randomized clinical trial where we looked at the development of insulin dependent diabetes, and auto-immunize disease where you were looking for as a marker of toxicity from the vaccine.

This study initially was published in the New England Journal of Medicine. And the group here, one group received four doses, one group received one dose, they were randomized, and we also have a control group that didn't receive any vaccine at all.

And I presented this slide before to the group. The group that got four doses of vaccine had the highest incidence of diabetes. The group that got three doses, I mean, one dose, had intermediate level. And the group here that received no vaccine had a low accumulative instance of diabetes.

We've actually published some of this in the British Medical Journal. More recent analysis, however, has shown statistically significant clusters. And this is one point I wanted to bring to you, is that we found that all the -- this is the group that received four doses of vaccine, starting at three months of age, shown here in the blue. And this is the group that received one dose at 24 months.

The curves diverge at around three years and a quarter after the vaccine is given. They are, otherwise, super-imposable. And then we see a statistically significant cluster occurring right here about three and a quarter years after the vaccine is given.

This is the group that got one dose of vaccine, starting at 24 months of life, and actually on average the vaccine was given around 26 months of life.

And this is a control group that got no vaccine. While there is some slight divergence here, the groups are essentially superimposable until, again, three years and a quarter after the vaccine is given, when we see a statistically significant cluster.

So, again, in two different analysis we see the same cluster, a statistically significant cluster occurring around three years and a quarter after the vaccine is given. And we think this is strong support for a causal relationship.

Furthermore we have done additional animal studies now, both -- these are in diabetes prone mice. Both groups got hepatitis B vaccine at birth, and at one month. However, the group in blue got HIB, DTP, AP, and inactivated polio vaccine starting around ten weeks of life, and they got three doses.

Again you see here the group that got the vaccines had the higher risk of diabetes, statistically significant. Again, this is strong support for a causal relationship.

There is a number of people out in the public that are calling for decreased number of doses of certain vaccines like the Pertossis vaccine, and the inactive polio vaccine, and our data supports this immunization schedule.

The last point I wanted to make, our last slide, was that during the Prevnar presentation, the group from Kaiser presented some data suggesting that they would expect 11 cases of diabetes in each of the groups of about 18,000 with a two year

followup.

This amounts to 58 cases per 100,000. This is what they would expect if there was no increased risk of diabetes from Prevnar. Well, Finland has the highest incidence of diabetes in the world, and we found only 30 cases per 100,000 when we looked at a two year followup.

So for some reason the Kaiser calculations were that they would expect twice the rate of diabetes in their groups than Finland, which has the highest instance of diabetes.

Clearly we think that there may be some miscalculations, or something is amiss, when they expect that if the Prevnar didn't cause diabetes they would have this very high rate of diabetes.

And so we think that this data should be made public so that we can further analyze this, and find out, and track the incidence of diabetes in the Prevnar groups to ensure the safety of Prevnar.

That is all I have today, to say, and I want to thank you for the time to speak to the committee. Any questions?

CHAIR DAUM: Thank you Dr. Claussen. I would like to move now to the open session. The FDA members could, at this point if they wish to, join us at the table.

And we are going to begin by calling on Dr. Karen Midthun to introduce the topic to us. Dr. Midthun?

DR. MIDTHUN: Good morning, and welcome. The topic

for today's Advisory Committee will be the lyme disease vaccine, LYMErix.

This vaccine was licensed in December of 1998 for the prevention of lyme disease in individuals 15 to 70 years of age. This vaccine contains recombinant outer surface protein A, so called OspA. OspA is a major outer surface protein of borrelia Burgdorferi, the bacterium that causes lyme disease.

Since licensure some members of the public have expressed safety concerns regarding this vaccine. What we will do today is review the available safety data, the cations that have been taken, and our plans for continued safety evaluation of this vaccine.

We will provide an overview of the safety data, both that which was available at the time of licensure, as well as additional safety data that have accrued since that time, from two major sources.

One source is the phase IV study, which was part of the post-licensure commitment, that SmithKline Beecham made at the time of licensure, and the second is adverse events which have been reported to the vaccine adverse event reporting system.

And what we would like is for the Advisory Committee to discuss the safety data, and the plans for continued safety evaluation of this vaccine.

And with that introduction I would like to introduce Dr. Patricia Rohan, medical officer in the Office of

Vaccines in the Center for Biologics, who will give the first presentation for FDA.

DR. ROHAN: Good morning, everyone. I would like to briefly review the pre-licensure safety data for LYMErix, and then to update you with respect to safety related activities that have been conducted since the time of licensure.

CHAIR DAUM: Could you adjust the microphone, Dr. Rohan, so that you speak -- that is probably a little better, thank you.

DR. ROHAN: First of all a little background. Lyme disease was first recognized in the mid and late 1970s, and has become the most common U. S. vector borne disease. It is endemic in several areas of the United States, with over 90 percent of the reported cases occurring in approximately 150 counties located in the northeastern and mid-Atlantic seaboard, and upper north central United States.

The peak disease transmission season in late spring through summer, is coincident with the feeding of the nymphal tick, the most common source of human infection.

The phase 3 pivotal efficacy study was a perspective multi-center, randomized, double blind placebo control trial. It was conducted over two lyme disease transmission seasons, and conducted at 31 sites in areas known to be endemic for lyme disease.

It enrolled approximately 11,000 subjects who were

equally randomized to either receive the lyme disease vaccine, or a placebo, which was the adjuvant alone. Vaccination was administered intra-muscularly at 0, 1, and 12 months, and the blinded observation period was 20 months.

There were several exclusion criteria, including the following. Physician diagnosed chronic joint or neurologic illness related to lyme disease, current disease associated with joint swelling or diffused joint or muscular pain, a known second or third degree atrial-ventricular cardiac conduction block, or cardiac pacemaker, pregnancy, or breast feeding.

As you can see the study had slightly more males enrolled. The group was overwhelmingly white, the treatment groups were similar in terms of age and gender, with the mean age 46 years.

With respect to efficacy, prevention of definite cases of lyme disease in the first year, following two doses of the LYMErix lyme disease vaccine, there was 50 percent efficacy seen. And in the second year following the third dose of LYMErix, 78 percent efficacy.

And there was no difference detected in lyme disease manifestations when vacinees were compared to placebo recipients.

Safety was monitored in a variety of ways. First of all, solicited adverse events were studied in a subset of 938 subjects via four day diary cards which were administered

immediately following each vaccination, and subjects were specifically queried so that their responses could be compared between groups.

There was also routine monitoring of all subjects, including clinic visits at 0, 1, 2, 12, 13 and 20 month. At each clinic visit the subjects were asked regarding the onset of any new adverse events since their last visit or postcard.

Safety postcards were used over the lyme disease seasons, five times in the first year, and three times in the second year, to gather more data during the actual transmission season.

After unblinding at month 20 an additional safety postcard was used at month 24 to collect additional safety data, and a data safety monitoring board was in place.

As you can see the results of the solicited adverse events from the diary card data showed that there were significantly increased rates of redness, soreness, swelling, arthralgia, fatigue and rash in the vacinee group versus the placebo group.

Also for adverse events in all subjects, which were reported within 30 days of vaccination, there were increased rates of injection site pain, injection site reaction, chills and rigors, fevers, and myalgia in the vacinee group, when compared to the placebo.

And I included data from the category arthralgia to

show you that there was not a statistically significant difference between vacinee and placebo overall in the 30 day period post-vaccination.

Also for adverse events occurring in all subjects, overall, more than 30 days after vaccination, there was no particular pattern of adverse events, differences between the placebo and vaccine recipients.

I also included data here to show you that the arthralgia rates, the arthritis, arthrosis, myalgia, and tendinitis were approximately the same in both the vacinee and placebo group for events occurring, again, more than 30 days after vaccination. The study also looked at subjects who had a history of lyme disease prior to entry into the study. There were 1,206 subjects who self-reported a history of lyme disease. That group reported increased musculoskeletal adverse events, whether they were a member of the vacinee, or the placebo group, when you compared them to subjects who had no history of lyme disease in those respective groups.

But there was an increased rate of musculoskeletal adverse events in the vacinees versus the placebo recipients, both of whom had a history of lyme disease in the immediate 30 day period following vaccination.

But that difference did not persist beyond 30 days, after 30 days there was no difference between vacinees and placebo subjects who had a history of lyme disease.

The study also examined western blot positivity at baseline. Baseline serology was examined in subjects who had a positive or equivocal western blot when they were seen at a clinic visit for suspected lyme disease.

And also all subjects who were tested in routine testing at month 12 or 20, if they were found positive they had retrospective analysis of their baseline sera, which was stored.

Using this approach 250 subjects were found to be positive by western blot out of 628 subjects tested. However, the nature and incidence of the adverse events did not differ between vacinees who were western blot positive, and vacinees who were western blot negative.

The overall lyme safety data base includes information on 18,047 doses of LYMErix, and this is the 30 microgram dose that is currently licensed. And the subjects exposed are 6,478, at least 15 years of age.

And I would point out that this group of subjects is largely composed of subjects in the efficacy trial of 5,400 and some patients.

This committee met May 28, 1998 and unanimously decided that the pre-licensure data supported the safety and efficacy of LYMErix given on a 0, 1, 12 month schedule in adults.

There were a number of recommended additional requests for post-marketing data. And at the time of licensure several post-marketing commitments were agreed to.

And I would like to briefly discuss a couple of these in more detail. But just overall to tell you that the phase IV study was planned to evaluate 25,000 vacinees. It was agreed that completion of a cellular immunity study, pre-clinical reproductive toxicity study, and a pregnancy registry.

The phase IV perspective cohort study, its main purpose is to evaluate LYMErix as a risk factor for new onset inflammatory arthropathy. In addition, various selected musculoskeletal and neurologic parameters are being compared, as well as serious adverse events.

Vacinees will be age and gender matched to controls at a ratio of one to three. The study was begun in January 1st, 1999, and as of November 6, 2000, approximately two years later, there are 2,568 vacinees under study, and I point out that this is about 10 percent of the planned 25,000 phase IV vacinees.

The phase IV cohort safety study, when it is completed, with 25,000 vacinees and 75,000 non-vacinees, will have an 80 percent power to detect doubling of events occurring at a rate of three per 10,000 in a non-vacinee group.

The cellular immunity study was designed as an exploratory study to describe the cellular response to OspA protein in humans. Additionally there was interest because it had been postulated that vacinees with a DR4 allele could be at risk for arthritis, based on several factors.

Lyme disease has been observed to persist for

months to several years, despite antibiotic treatment in a subset of patients with lyme arthritis. There has been an association reported between the DR4 allele, and treatment resistant lyme arthritis.

Also DR4 is one of several alleles that has been associated with disease severity in rheumatoid arthritis.

The study was completed, the results have been reviewed. And as I described initially, it is an exploratory study designed to describe cellular immune response in subjects exposed to OspA vaccine.

It is of limited power. However, it failed to identify an association between vaccination and arthritis in DR4 subjects.

I would like to acknowledge reviewers and other individuals at FDA who helped review this data over the last several years, and helped in the preparation of this presentation.

Now I would like to turn the podium over to the sponsors so that they might also address this data. And thank you for your attention, unless there are any questions.

CHAIR DAUM: Thank you, Dr. Rohan, for your presentation.

We have time for some questions from the committee. If there are any. Or, of course, our guests or consultants today. Dr. Griffin?

DR. GRIFFIN: With respect to the cellular immunity

studies it sounds, from your presentation, like they were confined to the DR4 positive subjects. Or was there a group that is DR4 negative that was being compared?

DR. ROHAN: No, and I think the sponsor will probably be discussing that in more detail. But it was a prospective study, and immune responses were described, and HLA typing was done, you know, after the subjects were enrolled. They weren't prospectively identified as DR4 necessarily.

DR. GRIFFIN: Okay, all right. So there will be information --

DR. ROHAN: Yes, and there will be more detail to that.

CHAIR DAUM: Ms. Fisher?

MS. FISHER: Are you aware of any other studies that are at variance with your conclusions?

DR. ROHAN: Which particular conclusions?

MS. FISHER: On the DR4 allele not being a risk factor.

DR. ROHAN: Well, as I said, this study was not designed to answer the question is the DR4 allele associated or does it confer increased risk to people who carry that allele when they receive an OspA vaccine. That was not the purpose of this study.

However, because it was being looked at we wanted to make sure that we didn't see some sort of association within

that study. But, as I said, it was of limited power, so it didn't happen to see an association.

But, you know, again that was not the primary purpose of the study.

CHAIR DAUM: Dr. Fagget, please.

DR. FAGGET: Yes. In the writeup it states that the current analysis, the small number of vacinees does not allow firm conclusions. Yet you say there was no association between the vaccine and --

DR. ROHAN: Right. One of the ways that you don't see an association is if the study is under power to see that association.

DR. FAGGET: That sounded like it was a firm conclusion that there was no association, that is why --

DR. ROHAN: Well, I tried to point out that the study was exploratory, at the beginning the study was exploratory, it was not designed to look to conclusively decide that question. It was to describe, in an exploratory manner, immune response.

CHAIR DAUM: Other questions or comments for Dr. Rohan from the committee?

(No response.)

DR. ROHAN: Thank you very much.

CHAIR DAUM: Thank you very much, Dr. Rohan.

We are now going to begin the SmithKline presentation this morning. We have, by my count, five speakers

scheduled on the sponsor's agenda.

I think what we will do is get started and see how things go, and perhaps take a coffee break in the middle, perhaps not. Let's see how much work we get done, and how many anxious faces I see around the table.

Our first speaker, as I understand it, is Dr. Kahn. You are on.

DR. KAHN: Well, good morning, Members of the Committee, FDA, and ladies and gentleman.

Over the next few minutes I will provide you the retrospective of the history of the development of LYMErix lyme disease vaccine recombinant OspA, and with an emphasis on the product safety.

My name is Clare Kahn, I'm vice president of North American regulatory affairs, responsible for vaccines.

GSK's presentation is essentially three parts. First Dr. Yves Lobet will address theoretical considerations of treatment resistant lyme arthritis, which we refer to as TRNA.

Dr. Francois Meurice will briefly review the data, the specific issues of interest, and the safety profile which supported the licensure of LYMErix two years ago.

And the third part of the presentation will address all activities, including the status and the findings of the post-licensure period. This presentation will be led by Dr. Bernard Hoet, and with a special presentation of the post-marketing safety

cohort study at the Harvard Pilgrim Health Care, which is under the independent direction of Dr. Richard Platt, and he is here today to present those status report. And then I will make short conclusions.

Well, maybe I can go quickly through this, as some of my slides will be essentially covered. Lyme disease is a multi-system disease caused by an infection with a spirochete borrelia burgdorferi, that is transmitted by the ixodes tick.

Since its recognition in 1975 lyme disease has become the most commonly diagnosed vector borne disease in the United States with over 100,000 cases reported to the CDC from '82 to '98.

During that time cases have increased by over 32-fold. The trend of an increasing incidence in some established endemic areas continues along with geographic spread to new areas.

This lyme disease is now a vaccine preventable disease, that disease is still on the rise. A few points on the disease itself. Early lyme disease is usually characterized by a rash, erythema migrans, fever, fatigue myalgias and arthralgias.

The early disseminated manifestations include secondary skin lesions, neurologic involvement, cardiac involvement, and musculoskeletal symptoms, usually consisting of migratory pain in the joints and the surrounding soft tissue structures.

The late stage disease, which occurs maybe months

to years after the initial infection, and may be manifest by chronic conditions, including chronic arthritis, neurologic abnormalities, or skin conditions.

There may be permanent sequelae and, in particular, the late neurological involvement is associated with a chronic, slowly progressive disease.

Since there is no practical enzootic control of infection, sorry, control of enzootic infection, or to prevent its spread, and since personal measures are largely and infrequently implemented, the introduction of a preventive vaccine was deemed a critical approach to the protection against lyme disease in the United States.

A few words on the vaccine. And LYMErix was developed to address the public health need. It is a non-infectious recombinant vaccine developed by GSK Biologicals. It contains the lipo protein OspA, which is an outer surface protein of the organism, as expressed in e-coli.

Each half mil dose contains 30 micrograms of the L-OspA absorbed onto a half a milligram of alum. And the primary immunization consists of three doses of LYMErix given intramuscularly at 0, 1, and 12 months in those aged 15 to 70 years.

Now to the historical perspective, and I have shown in this slide, from 1993 where the pre-IND meeting, up until launch in January of '99. The orange boxes, to make life easy to

review, is FDA meetings, and the green are reviews with the VRBPAC.

The R&D was submitted in February of 1994, and the VRBPAC was convened in June of that year to provide advice on the overall development of the vaccine.

So that advice included a review of the lyme disease information itself, and recommendations for pivotal development. This included case definition, primary and secondary pivotal study endpoints.

The requests for a two-year followup for safety and efficacy, and the inclusion of patients with previous lyme disease. Phase III plans were then, after agreement with CBER at the end of phase II meeting, that is in December of '94, and thereafter a two-year pivotal efficacy study commenced, Lyme-008, it ran for the full two years, and included over 10,000 subjects.

So during the conduct of the pivotal trial there was another VRBPAC meeting, and during this time more advice was given. First on the basis for going forward with pediatric development, and then further discussions, essentially, of theoretical safety concerns, including the potential for L-OspA vaccine to either exacerbate lyme disease pathology, to mask lyme disease presentation and diagnoses, or to induce auto-immune arthritis.

And you will see, from the subsequent talks, how these elements were incorporated into the development plan.

Based on all the advice received, and the demonstrated efficacy of the Lyme-008 study, the pre-PLA meeting was held with CBER in January of '97, and the PLA/ELA was submitted in September of that year.

During the review period Dr. Steere-Root published their paper, presenting their hypotheses that OspA may be responsible for TRLA. So when the VRBPAC met to consider the data package for approval, this topic played a significant part of the discussions at that time.

And at that time LYMErix was considered safe and effective, and thereafter approval was gained in December of '98, and the launch of the product was in January of 1999.

Moving on to the post-licensure period, GSK has engaged in both specific commitments, as well as the standard post-marketing requirements for safety assessment. These will be addressed by Dr. Hoet.

First the commitment, it was already reviewed briefly by Dr. Rohan, a post-marketing cohort safety trial was initiated at Harvard Pilgrim. The study started about a year ago. We have submitted three quarterly reports, but they do indicate a rather low uptake of the vaccine at that center. And you will hear what steps are put in place to address that.

The study on the cell mediated immunity, which was also discussed previously, was conducted and submitted in December of '99. And, finally, studies to asses safety in those of child-

bearing potential, were conducted.

First the repro-toxicity study in animals was conducted, and the report submitted a year ago. And pregnancy registry was established within the post-marketing surveillance methods.

And then moving on to the post-marketing surveillance, besides the usual reporting mechanisms, we had introduced two additional measures at CBER's request.

The first was to expedite all reports of musculoskeletal and neurological events, within 15 days, regardless of seriousness. This would, normally, only serious adverse events would be treated in this fashion. But special attention was given to these adverse events of interest.

And, secondly, a letter was sent to investigators of all completed and ongoing clinical trials which reinforced to them the requirements for reviewing and reporting adverse events from subjects who had been previously in those clinical trials.

And it also requested, over and above the normal requirement, that all reports be reported regardless of attribution, particularly if the patient was overly concerned, was concerned about it.

So all regulatory activities and commitments are completed and/or in place. And, as you will hear later, a review of the post-marketing surveillance shows that the most frequently reported adverse events involved reactogenicity with symptoms

already described in the product label.

But these reports from the post-marketing are such that they allow us to did you, within certain individuals, that symptoms occur concomitantly. And, secondly, very rare reports of hyposensitivity have been received.

So, in conclusion to my talk lyme disease is a vaccine preventable disease, the disease is still in the rise. It is associated with chronic morbidity and sometimes permanent sequelaeing.

Collaborations with CBER and the VRBPAC during the last decade have guided the vaccine through development to licensure. And I can say, upfront, before the talks, that to date the available data from the post-marketing surveillance, the commitments, and the additional clinical trials, are in keeping with the pre-licensure safety profile.

So at this point I would like to turn over to Dr. Yves Lobet, who will talk about theoretical considerations of TRLA.

DR. LOBET: Thank you, Dr. Kahn.

Before we go into the presentation of the clinical data, I would like now to address the theoretical concern raised in the 1998 Advisory Committee meeting, that vaccination with OspA could be responsible for the induction of treatment resistant lyme arthritis, a condition that has been observed in a few lyme disease patients.

This theoretical concern was raised after the predication of the paper of Gross et al, which working hypotheses I would like to present now.

One can summarize the hypotheses proposed by Gross et al in three points. First, they proposed that treatment resistant lyme arthritis is an autoimmune disease that could be initiated after a natural infection by B burgdorferi.

Secondly, first reactivity between OspA and LFA1, a protein present in some human cells, would explain the autoimmune nature of the disease. Finally, HLA-DR4 individuals are at risk of developing TRLA after natural infection.

Before going any further in the discussion, let's see how this hypotheses translates in the natural situation.

When borrelia burgdorferi is injected by ticks in a human body, it could migrate into various tissues. In some individuals the bacteria will enter one or a few joints. At this site it will initiate the disruptment of an inflammatory process, as observed also, when borrelia is present in other tissues.

The bacteria will also start expressing OspA when in the joints. This molecule being present on the surface of the spirochetes, an immune response is triggered against it.

In this process OspA specific t-cells are primed and stimulated. This stimulation is the result of interactions between the t-cells and fragments of OspA.

The nature of the sequence of this epitope vary

from individual to individual. And is defined by the HLA genetic background of these individuals.

In the case of HLA-DR4 individuals, one of the epitopes of OspA presents homologies with an epitope of LFA1, the human protein.

Gross et al has shown that these two epitopes are going to stimulate OspA specific cell lines. As a consequence, after the disappearance of OspA, the FLA1 epitope would be able to continue the stimulation of OspA specific t-cells.

This stimulation would contribute to the perpetuation of the inflammatory response within the joint. Provided that this information process could be, by itself, responsible for arthritis, this would explain the long-lasting disease observed in patients even after antibiotic treatment.

Next slide. This is the hypotheses presented by Gross et al, and I would like now to discuss it and address the following points.

There are some indications in this proposal, and I would like to present them to you. Secondly, I will discuss with you whether this hypotheses is applicable to vaccination with OspA. And, finally, I will present shortly some results.

So, what are the limitations of this hypothesis? First of all, the autoimmune nature of treatment resistant lyme arthritis is still questioned. Indeed, not everyone agrees that borrelia burgdorferi is absent from the affected joints of

individual of treatment resistant lyme arthritis.

If, indeed, despite antibiotic treatment borrelia is still present in the joint, the mere presence of the bacteria could explain the prolonged arthritis.

Secondly, the core of the Gross et al hypothesis, that LFA-1 is the auto-antigen involved in the suspected autoimmune treatment resistant lyme arthritis, is based on sequence homology, and in vitro crossreactivities between this molecule and OspA.

However, two recent publications have shown that the demonstration of sequence homology and in vitro crossreactivity between a foreign protein and an auto-antigen, is not sufficient to conclude that an autoimmune disease will take place. Other unknown elements have to be present to initiate an autoimmune process.

The OspA LFA-1 crossreactivity, therefore, does not demonstrate that OspA is responsible for the induction of autoimmune disease. One should also remember that after infection, when borrelia is in the joint, many proteins are presented to the human immune system.

May I have shown that this -- that several of these are morphologies and in vitro crossreactivities with human proteins, and could therefore be responsible for a hypothetical autoimmune reaction.

Finally, there is a discrepancy between the

restricted distribution of the symptoms, that is a few large joints are affected by treatment in lyme arthritis, and the universal presence of hLFA-1, that is present on lymphocyte in inflammation sites.

Next slide. Even if the hypotheses of Gross et al is confirmed in the future we do not believe that it applies to vaccination. Indeed, as mentioned in the publication, there are at least two requirements that are necessary for the development of treatment of resistant lyme arthritis.

First, OspA is to be present in the joint. During natural infection, indeed, this protein is expressed by OspA within that tissue. However, there is no reason to think that OspA migrate to that location after vaccination.

The second requirement is that for TRLA to develop an inflammatory process, an inflammatory milieu has to be present in the joint. Once again, we do not believe that this takes place after vaccination.

There is, therefore, no reason to believe that vaccination with OspA will reproduce the conditions identified by Gross et al, required for the development of treatment of resistant lyme arthritis.

Give me the next slide. Finally, I would like to share with you results which we have obtained from C3H mice showing that these experiments, that these requirements are indeed not met after immunization with OspA.

This strain of mice is known to be susceptible to the development of arthritis after infection with borrelia burgdorferi. And we have confirmed this, in this experiment. We have shown the presence of clinical arthritis 28 days after inoculation with borrelia.

On the other hand, when C3H mice were vaccinated with OspA, we found no sign of arthritis. Indeed, neither joint swelling, nor signs of inflammation have been observed 28 days after injection. Further, no OspA has been detected in the analyzed joints.

The primary conclusions of the experiments are that, indeed, OspA immunization does not create the environment required for development of treatment resistant lyme arthritis.

Next slide. In conclusion, on the basis of both a theoretical analysis of the treatment resistant lyme arthritis hypotheses of Gross et al, and the results of clinical experiment, we found no evidence supporting that vaccination with OspA will initiate the development of treatment resistant lyme arthritis.

This observation has been reviewed and conclusions agreed upon by a panel of independent experts in autoimmunity.

Finally, it should be noted that since 1998 no new data has been published to further confirm the hypothesis of autoimmunity treatment of resistant lyme arthritis.

Thank you for your attention, and we now leave the stand for Dr. Francois Meurice, who will present you with the

clinical data that we have collected prior to licensure of LYMErix including those indicating that no increase of incidence of arthritis was observed in HLA DR4 vaccines.

CHAIR DAUM: Thank you very much, Dr. Lobet. I would like to invite the committee at this time to ask questions, and ask the speakers to allow me to introduce the next speaker after you are concluded.

So, and also before we take too many questions, I would like to inform the committee of something I didn't realize, and that is that the slides for the sponsor's presentation were put at your seat this morning.

So that might make note taking and following a little bit easier. Dr. Fagget, I saw three hands. I saw lots of hands. Okay, we will just go right up the row, here. Dr. Fagget?

DR. FAGGET: Thank you for a very eloquent presentation of the previous speaker. Could, indeed, what we see be a vaccine failure? Is that another possibility here in terms of the arthritis?

DR. LOBET: Could this be a what?

DR. FAGGET: Vaccine failure, so that any inflammatory process that was there was --

DR. LOBET: The clinical data will be presented by Dr. Francois Meurice. Maybe it is better to discuss this after his presentation.

What I addressed is, really, the theoretical

concern of the hypothesis, based on this hypothesis.

CHAIR DAUM: Could you revisit your question, Dr. Fagget, when we get the clinical information?

DR. FAGGET: Yes.

CHAIR DAUM: Dr. Griffin, then Dr. Kim, Dr. Snider, and Dr. Kohl.

DR. GRIFFIN: I am interested in your mouse experiments with the C3H mice. And I have a couple of questions.

First of all, is it known whether the susceptibility of C3H mice is due to an HLA class 2 determinant?

DR. LOBET: This experiment doesn't demonstrate or infer or confirm the autoimmune nature of the disease.

DR. GRIFFIN: No, I'm just trying to -- I'm only trying to identify how relevant the mouse experiments are to the questions that we have in humans.

DR. LOBET: No, it is not thought to be, the susceptibility is not thought to be related in special HLA typing --

DR. GRIFFIN: Is it not?

DR. LOBET: No.

DR. GRIFFIN: And then I also have another question, and that is with respect to whether, since the development of autoimmune disease after, as a consequence of infection is obviously an extraordinarily complicated process, in the situations in which that is -- when the mechanisms even begin

to be understood.

Is there any evidence that if you take the mice that have developed arthritis after infection, and then give them OspA that you exacerbate the arthritis?

DR. LOBET: No.

DR. GRIFFIN: Those experiments have been done and they are negative?

DR. LOBET: I should go back and check if these experiments have been done, because --

DR. GRIFFIN: Because it is a little different than just giving OspA, which was going to be presented --

DR. LOBET: Absolutely, fully agree.

DR. GRIFFIN: -- and everything, in a totally different way.

DR. LOBET: Fully agree. But, again, in this case we did not inspect autoimmune arthritis taking place in those mice. What this experiment shows is really that the conditions that are required, as they have been defined by Gross et al in their paper, for the autoimmune disease to take place, are not met after vaccination.

That is, the presence of OspA in the joints, and the induction of an inflammatory milieu there. It doesn't address the autoimmune nature of the disease.

CHAIR DAUM: But could you clarify Dr. Griffin's question, Dr. Lobet, before we move on? And that is, are the

experiments done, and the answer is no, or is the answer --

DR. LOBET: The answer --

CHAIR DAUM: -- experiments not done?

DR. LOBET: The experiment has not been done the way it has been presented.

CHAIR DAUM: Thank you. Dr. Kim, please?

DR. KIM: I think we have seen publications, and also you indicated the mapping of OspA for HLA DR and LFA regions, crossreacting areas.

Are there any information available about protective epitope of OspA, whether that is overlapping with these epitopes, or are there different regions of OspA?

DR. LOBET: The -- one of the properties of OspA is that it overlaps three areas of the acetomino region of the molecule, and does not overlap with this OspA crossreacting epitope.

CHAIR DAUM: Thank you. Dr. Snider, Dr. Kohl, Dr. Diaz, Dr. Estes.

DR. SNIDER: My questions were similar to Dr. Griffin's, and it had to do with the C3H mouse model. The questions were whether one hundred percent of the mice developed the autoimmune arthritis after infection with borrelia burgdorferi.

And whether, if not one hundred percent do, whether giving OspA before or after the infection increased the frequency

of it, or if one hundred percent do, whether giving OspA before or after the infection increased the severity of it?

And I guess, based on the answer I heard earlier, there are no such experiments, but I would like confirmation.

DR. LOBET: Let me first repeat that this is not autoimmune arthritis that has been induced in those animals. We don't expect autoimmune arthritis to take place there.

This is, really, what we wanted to evaluate there is whether the requirements defined by, in the hypothesis presented by Gross et al, could be met after vaccination with OspA.

Now, indeed, one hundred percent of the animals developed arthritis after inoculation with borrelia.

DR. GRIFFIN: Can I just ask a follow-up, then? Then I don't understand the relevance of the model. If there is no autoimmune component to the lyme disease borrelia burgdorferi induced arthritis in the mice, then I don't see how the -- giving them the vaccine addresses the question.

DR. LOBET: One of the question that could be raised after -- so the question is whether the vaccine could induce autoimmune arthritis.

One of the requirements to induce such a disease, as presented by Gross et al, is that you need to have both OspA present in the joint, and that an inflammatory process takes place there.

What we wanted to show in this model is that those two requirements, I mean, we wanted to address whether those two requirements could be met after vaccination with OspA. This is independent of an autoimmune response.

So it means that if you have crossreactivity, simply crossreactivity, either on the basis of sequence homologies, or in vitro crossreactivities between t-cells, this is not enough to explain the induction of an autoimmune process.

You need to have other requirements, such as an inflammation process taking place at the location of this phenomena. So what we wanted to demonstrate here is that those requirements, necessary for the development of autoimmune arthritis in humans are not met.

DR. GRIFFIN: But it could be done in any kind of animal, or mouse. The C3H has nothing to do with it?

DR. LOBET: The C3H, the strain of C3H mice has been used because we know that those animals are susceptible to arthritis after infection.

DR. GRIFFIN: But it is not autoimmune?

DR. LOBET: No, it is not autoimmune. No, I fully agree with you. No, we never said this is an autoimmune phenomena.

CHAIR DAUM: Is the confusion here the word autoimmune? That is to say, we have a model in which the organism causes infection and arthritis.

DR. LOBET: And arthritis.

CHAIR DAUM: And so the question, then, is does the vaccine cause arthritis in this model, any kind of arthritis. And the answer, at least, is no?

DR. LUFT: I think the question is whether the model is reflective of human disease or not.

CHAIR DAUM: That is a separate -- that is an issue that needs to be discussed.

DR. LUFT: Yes, indeed. These animals do become infective, and as an infectious model it works. If you try to see whether a vaccine prevents infection, it could be a very fine model.

But to try to understand the pathogenesis of human disease, it may not be a very good model.

CHAIR DAUM: As is true of any animal model, it always has limitations.

DR. LUFT: It has its limitations.

CHAIR DAUM: Let's hear from Dr. Kohl, please.

DR. KOHL: I think that is my point as well, it doesn't seem to be a relevant model for treatment resistant arthritis, or autoimmune arthritis.

DR. LOBET: I fully agree with you. I mean, this is not an autoimmune model.

DR. KOHL: That is what I was saying. Now, the arthritis gets better by itself, or gets better with antibiotic

treatment?

DR. LOBET: Excuse me?

DR. KOHL: In the mice, is the arthritis self-limited, or does it respond to antibiotics?

DR. LOBET: It is self-limited.

DR. KOHL: It is self-limited. So it is totally not related to what we are talking about, it seems.

CHAIR DAUM: Thank you. Dr. Diaz next.

DR. DIAZ: Thank you. I recognize that what you were trying to show, obviously, has nothing to do with interactions between the vaccine and autoimmunity in humans.

But at the same time commented that if you give these mice OspA, that you have -- there is no detectable measure of OspA in the joint, correct?

DR. LOBET: We haven't seen OspA in the joints. Where we were able to detect it in the proximate muscles, where there has been injected.

DR. DIAZ: In the mice that were given borrelia, and developed arthritis, secondary to that infection, were you able to detect borrelia in the joint, and OspA production in the joint?

DR. LOBET: Those analysis are still ongoing. So far we haven't seen OspA in this location. The reason being that, one explanation to that, which we are still working on this aspect, is that the number of spirochete going to the joint is

usually very small.

And we use a small amount of spirochetes, around 1,000 spirochetes, that have been injected not close to the joint. So to make more closely the natural situation.

CHAIR DAUM: Thank you. Dr. Estes, Dr. Stephens, Dr. Luft.

DR. ESTES: I have a basic question about the organism. Are there different strains of this organism that have different disease capability, whether it is in mice or in humans, is that known?

DR. LOBET: There are some -- right now there are some groups who have identified differences in strains that -- apparently different pathogenesis, pathologies, but this is really ongoing work.

CHAIR DAUM: Thank you. Dr. Stephens?

DR. STEPHENS: I would like to just pursue a different mechanism related topic. And that is, lipo-proteins are known to be very potent stimulators of total receptors, for example.

DR. LOBET: Yes.

DR. STEPHENS: Data that has come out, I guess, since the vaccine was approved.

Do you have any information about the ability of OspA, as a lipo-protein, to generally stimulate cytokine production or other immune reactions?

DR. LOBET: It has been known for quite a long time, since the early '90s, that OspA is able, by itself, to induce both pro and anti-inflammatory cytokines. And there are multiple papers addressing this point.

CHAIR DAUM: Thank you. Dr. Luft, then Dr. Ferrieri.

DR. LUFT: Yes. I would just like to kind of take up where Dr. Estes left off, about different strains. That the LFA homology, I guess it was pointed out in that original paper, seemed to be with OspA from borrelia burgdorferi sensu stricto, it wasn't shared as to the same extent with OspA from other geno species of borrelia.

Have you, or anyone in the company, immunized others, patients in the United States, or in Europe, with these OspA types of absceleri, or goreneri or animals? And have you seen any differences in reactivity, or in any -- either laboratory or clinical manifestations?

DR. LOBET: Yes, we have indeed vaccinated people with goreneri and absceleri. We haven't seen any clinical or laboratory differences between people immunized with sensu stricto OspA only.

CHAIR DAUM: Dr. Ferrieri, please.

DR. LUFT: I would just like to --

CHAIR DAUM: Do you want to follow-up, Dr. Luft? Okay.

DR. LUFT: And how large has that been, is it something that we will be able to see in a statistical type of manner, that there are no differences between that?

The question I really have, and it goes back, actually, to what Dr. Stephens said as well. This whole LFA business may be a red herring, but there may be a phenomenon that occurs.

This is a very unique protein, it is a lipo-protein that has -- that is very immunoreactive. Actually probably one of the first lipo-proteins that have been injected into people as part of a vaccine.

So there may be other phenomenon. And I think one of the ways that we start to discern these differences is if we see very similar types of material, whether it is from OspA, from borrelia absceleri or goreneri, giving us same phenomenon that you see with burgdorferi.

I think you can say this LFA thing, maybe that is a red herring, because there are differences in the sequence in that particular region. But we still have to deal with the lipidation issue, which we haven't really focused on, for whatever reasons.

But, so, is it large numbers of patients, or is it small numbers of patients?

DR. LOBET: Can you first clarify what phenomenon you are relating to? I mean, what kind of analysis are you referring to, that compares OspA sensu stricto to the other ones?

DR. LUFT: I just say clinically are there any differences?

DR. LOBET: No, there is not.

DR. LUFT: And I'm just saying, do you have -- is it -- do you have enough power, statistically are able to make that answer in a way that really is with conviction and belief, or is it something that says, we did a handful of patients here, and a handful of patients there.

I just want to know how --

DR. LOBET: No, with several tens of patients, a few hundred patients that have been vaccinated.

DR. LUFT: A few hundreds patients with the different --

DR. LOBET: Yes.

CHAIR DAUM: Thank you.

DR. LOBET: Nothing particular were observed in those as compared to what observed in the sensu stricto only vaccinated patients.

CHAIR DAUM: Thank you, Dr. Lobet. I'm going to call on Dr. Ferrieri for one last question, and then ask the sponsor's presentation to continue.

We can return to these topics, we will have time for discussion, and the committee is clearly been piqued by your presentation, and that is a good thing. Piqued with interest.

Dr. Ferrieri, please.

DR. FERRIERI: Back to the mouse model, three very brief points. What was the amount of OspA given to the mice, what was the nature of your assay for OspA, was it Elisa, was it a genetic assay, and what were the limits of detection of OspA in your assay?

DR. LOBET: All right. We used one microgram of OspA twice, which is what we use, usually, to raise the immune response able to protect mice, and similar to what is observed in humans.

OspA has been detected by chemistry. And at this point we have not yet -- we have seen in the slide, this is still ongoing work, and don't have yet the level of reduction of OspA, the threshold of detection of OspA.

CHAIR DAUM: Thank you very much, Dr. Lobet.

Could we continue, then, with Dr. Francois Meurice?

DR. MEURICE: Thank you, good morning. My presentation will address the LYMErix safety information that was available for licensure.

I will start with a brief review of the clinical data that were available for licensure, then I will give you additional information on the safety which was collected from the large pivotal efficacy study.

And I will touch on several areas of special interest that were prospectively addressed in the development of the vaccine, which are the influence of vaccination on lyme

disease manifestations; patients with previous lyme disease history, autoimmune arthritis, HLA type, and the musculoskeletal symptoms, as well as the neurology and cardiac events.

For phase 1 clinical studies were conducted in Europe, essentially, to select the formulation of the vaccine. And that is how lipo-protein OspA candidate was selected for further development.

Among the phase 2 trials, two studies were of particular interest and conducted in the United States. That is lyme-005, which is a dose range placebo control study, where HLA typing was performed, and 007 which addressed, especially, the safety of the vaccine in patients with previous lyme arthritis.

Next. Most of the safety data, as was mentioned, come from the pivotal efficacy study lyme-008, which was followed up by the same cohort continuing for another year safety follow-up.

Next one. So at the time of the BLA 16 studies were either completed or ongoing, and the data were submitted on about 6,500 subjects who had completed studies, and who received a final formulation of the vaccine.

So I will not go into a lot of detail, since you heard this in the previous presentation by Dr. Rohan, the pivotal efficacy study lyme-008 was double-blind placebo control efficacy study, including healthy individuals between 15 and 17 years of age, from lyme endemic areas.

And the exclusion criteria, as were mentioned, are listed here below.

So schematically in that study people received two doses of vaccine one month apart, were followed up for full lyme disease transmission season. A block sample was collected systematically in everyone, at the end of the season, and at month 12 the third injection was given.

People were followed up in the double blind manner until the end of the transmission season at months 20 the last blood sample was collected. However, as I said, lyme-013 continued the follow-up of this cohort, and the data that were reviewed in the BLA covered up to month 24.

I think you had information about how the adverse events were collected in that study, both as unsolicited adverse events, and we clarified those occurring with an early onset, or with a late onset.

A subset of the cohort, about 900 subjects had diary cards to collect solicited symptoms during the first four days after vaccination. And since this was an efficacy study, symptoms suspect for lyme disease were obviously collected in a very aggressive manner, and these were also combined with the data base of adverse events, whenever lyme disease was not confirmed.

So as far as unsolicited adverse events occurring within 30 days, we had injection site reactions, mostly pain. And among the general symptoms, which were statistically significant

in the vacinees, we had fever, influenza-like symptoms, myalgia, chills and rigors.

For the unsolicited symptoms with onset more than 30 days after any dose there was no statistical differences between placebo and vacinees. Also looking at adverse events after successive doses of the vaccine, there was no increase in the reactogenicity after the following doses.

In terms of local and general solicited symptoms, we again had the local symptoms at the injection site, we had several flu-like symptoms including fatigue, and arthralgia, a rash was also observed.

There was no statistical difference for headache or for fever. And the mean duration of the general solicited symptoms was one to eight days, depending on the symptoms, with a range of 236 days.

Serious adverse events were according to the classical definition. On top of this in that study pregnancies and arthritis or arthralgia lasting for more than 30 days were recorded in a similar manner, to have a good follow-up, in real time, about what is occurring for this specific symptom.

We had 581 vacinees, and 586 placebos reporting serious adverse events. When looking at those by body system there was no statistical difference. There were 14 of them in the vaccine group, and 15 in the placebo recipients, which were designated as related or possibly related to the vaccine, and no

deaths were attributable to the vaccine.

So the safety conclusions, as far as unsolicited AEs was onset less than 30 days. There were more reactions in vacinees and in placebo, that was not the case for those unsolicited AEs with onset more than 30 days after vaccination.

In terms of solicited AEs there was a very high reporting rate of adverse events, both in vacinees and in placebo groups. Since you see at least 82 percent of the placebo group reported at least one symptom.

Don't forget that this was a very scrutinized follow-up. Soreness was the most common local symptom, headache and fatigue were the most common systemic symptoms, and less than 5 percent of the solicited symptoms were rated as severe.

Finally, in terms of serious adverse events, as I said, no difference between vaccine and placebo.

Now I will touch on a few areas of special interest which were identified at the VRBPAC before we started the study.

The first one is the influence of vaccination on lyme disease manifestations. What we could conclude from this trial is that we saw no interference with the ability to confirm the lyme disease diagnosis by culture, PCR, or western blot.

The vaccination provoked no mask, no attenuation or alteration of the clinical presentation of lyme disease. There was no increase in the rate of asymptomatic infection. Actually the vaccine was highly protective.

Again, these cases, 83 percent in the first year, 100 percent in the second year, against asymptomatic infection.

There was no effect, in particular, on the duration of the erythema migrans, and no influence on the management of the treatment of the breakthrough cases in vacinees.

A second area of special interest are the subjects with previous lyme disease. And in particular we wanted to answer the question: Do subjects with previous lyme disease have more symptoms than those who did not have previous lyme disease?

We assessed lyme disease histories in two ways, one was in patients self-reporting lyme disease, and the other one was by a more objective criterion, which was western blot positivity at baseline.

Next. Looking at adverse events in subjects self-reporting previous lyme disease, in general for these symptoms, as was mentioned before, vacinees with a history of lyme disease reported more symptoms for these categories than vacinees with no history of lyme disease.

Next. This was generally seen also in the placebo group with one exception, which was early musculoskeletal symptoms for which, in that case, placebo recipients with history did not report more of those symptoms than those with no history.

If we look at the figures we can see that, in general, these are the details, and the importance, the statistical importance of the differences are pointed here.

Now, when looking at the more objective way of assessing previous lyme disease, which is western blot positive at baseline, we didn't see these differences. So there was no increase in any of these symptoms in those subjects.

And, again, here are the detail data if you want to refer to it.

So in summary patients with self-reported lyme disease, in those we saw an increased incidence of AEs in both the vacinees and the placebo recipients. One exception to the above was seen for the early musculoskeletal adverse events, where this increased incidence was not seen in the placebo recipients.

The western blot, while it showed that nature and incidence of any of those adverse events did not differ between the western blot positive at baseline, and the western blot negative at baseline, be it in vacinees or in placebo subjects.

So western blot confirmed previous lyme disease had no impact on the safety profile, and probably the previous self-reported history has not, either.

What about induction of autoimmune arthritis? First of all, looking at the general incidence of arts in that study, there was no difference in terms of the incidence rate in vacinees of placebo, be it cases of arthritis with onset within less than 30 days after any dose, or within more than 30 days after any dose.

We did prospectively address HLA typing and

musculoskeletal symptoms in two studies. So this is, obviously, in line with what was discussed by Dr. Lobet previously, specifically the HLA-DR4 individuals who could be at higher risk of developing treatment resistant lyme arthritis after natural infection, this increased with vaccine or not.

In Lyme-005 most of the subjects in that study, more than 300, were tested for the HLA-DR4 and two types. As you can see, about a third of the population involved in the study was DR4 positive.

We had four cases of unspecified arthritis in that study. One in the placebo group was DR4 positive, and one in vaccine group was also DR4 positive. The two others were negative.

Another attempt to clarify this issue was done in Lyme-008, where two subsets of subjects were analyzed. In the first subset 85 consecutive samples at one site were collected in 41 vacinees and 44 placebo recipients, and a similar HLA profile was seen in vacinees with, versus without pain or inflammation at the injection site.

A second subset looked at the problem by the other way, and identified twelve subjects from the entire study population with unexplained arthritis or tendinitis.

For nine out of those twelve HLA typing was available. One out of the four in the vaccine group was HLA-DR4 positive, and one out of the five of those subjects in the placebo

group was DR4 positive.

So in conclusion we didn't find any evidence, from these two studies when we did HLA typing, but there was a link between vaccination and the development of musculoskeletal or inflammation symptoms.

Finally, neurology and cardiac events. Reviewing those cases, no difference was seen in any of the neurologic or cardiac events between placebo and vacinees. And I should remind you that this large study was carefully monitored by DSMB, all these adverse events of interest, especially rheumatology cases, and neurology cases, were carefully reviewed by a panel of experts.

So in conclusion, a large body of safety data was available, was accrued prior to licensure, and this revealed an acceptable safety profile in the clinical trials, although we did see moderate reactogenicity with this vaccine.

There is no clinical evidence, including from the HLA typing that was done, supporting the theoretical concerns.

Finally, vaccination demonstrated efficacy in definite cases, and asymptomatic cases of lyme disease. Therefore LYMErix was considered safe and effective, and was approved for the prevention of lyme disease.

Thank you very much.

CHAIR DAUM: Thank you, Dr. Meurice. I will take a few questions from the committee before we move on. Dr. Estes,

Dr. Fagget next.

DR. ESTES: Could you tell me what is the predictive value of the western blot for diagnosing previous lyme disease?

DR. MEURICE: I don't know the answer to that question. I guess what we did in the study was, indeed, to look systematically at western blot at months 12 and 20 in all subjects, and those which were positive we went back to baseline.

The same thing when patients came up with symptoms of lyme disease we had western blot taken. For all those cases which came up with other symptoms like erythema migrans which was the most common, we also performed biopsy, and look at culture, and PCR.

The culture and PCR were able to detect an additional 15 to 20 percent of the cases which were not detected by western blot sera conversion. That is the indication I can give.

DR. ESTES: Does anyone else know the answer to that? Does the western blot --

DR. DATTWYLER: I am on the CDC serology committee, and that is not known. I mean, it is certainly the positive predictor value is not one hundred percent by any means.

The other thing that should be mentioned is that the ability of this vaccine to confuse the diagnostics is a real problem, and that there are publications now stating that in

vaccinated uninfected individuals, that you can get false positive western blots by CDC criteria.

CHAIR DAUM: But, Dr. Dattwyler, the question that, at least I think I hear Dr. Estes asking, is about the presentation. And that is to say that people who believed they had lyme disease before were stratified into two groups. One self-reported and one had western blot positivity. Presumably some time remote from when they actually had the lyme disease.

So the question is, among lyme experts such as yourself, what do you think of that stratification? I think that is the real question.

DR. DATTWYLER: It is not unreasonable. The difficulty with immune response it depends on how long after you've been successfully treated, and the timing of the infection. If one is treated very early for erythema migrans, and you don't develop a mature immune response, then your western blot is negative.

On the other hand if you develop full-blown lyme arthritis, and you have been successfully treated, you may remain sera positive for years afterwards.

So it is a rather difficult issue, and you have to stratify by the stage of the disease, and when it was treated, and how it was treated.

CHAIR DAUM: Thank you very much. I have Dr. Fagget next, and then Dr. O'Fallen.

DR. FAGGET: Yes. In your conclusion you state 78 percent efficacy for definite cases of lyme disease, correct? And one hundred percent asymptomatic.

DR. MEURICE: Correct.

DR. FAGGET: Also you stated that there is no mask attenuation, alteration of clinical presentation of lyme disease with vaccination, correct?

DR. MEURICE: Correct.

DR. FAGGET: So, indeed, could TRLA be vaccine failure? I go back to my previous question.

DR. MEURICE: Well, we carefully looked at the breakthrough cases in that study, obviously. And looking at their clinical features there was really no difference with the cases that were observed in the placebo group. So the clinical manifestations were identical, and the treatment of those cases was not more complex.

DR. FAGGET: My question, though, is relative to treatment resistant lyme induced arthritis.

DR. MEURICE: We have not seen any case of treatment resistant lyme arthritis.

DR. FAGGET: Well, over what time period did you look at the subjects?

DR. MEURICE: We looked for two years of follow-up.

DR. FAGGET: Thank you.

CHAIR DAUM: Thank you, Dr. Fagget. Dr. Kohl --

DR. MEURICE: -- actually an additional year of follow-up the same cohorts continued safety follow-up for an additional year.

DR. COYLE: I just wanted to get clarification on the group in your pivotal study that was said to have prior lyme disease.

I'm assuming that the group that was classified retrospectively based on the western blot, when they first came in, that was just an IgG western blot, correct, no one was counting IgM?

DR. MEURICE: Well, there was an IgM western blot if ever they presented with symptoms suspect of lyme disease, but then the baseline was, indeed, IgG western blot.

DR. COYLE: In the patients who self-reported that they had had the lyme disease, that particular group, was there an attempt to verify that, or to classify them by the prior syndrome, was that probably EM physician reported, or is that simply -- was there any breakdown of prior arthritis, neurologic, or was that simply taken at face value?

DR. MEURICE: No. We wanted to do it the largest possible way, so anyone who was self-reporting lyme disease we didn't ask for medical records, we didn't go through.

DR. COYLE: So was any investigation done of the basis for what the patient reported their syndrome was, or not?

DR. MEURICE: Well, the symptoms were collected as

part of the medical history of those subjects, but we didn't do any stratification based on that.

DR. COYLE: So there was no breakdown, you have no idea how many that was EM, they said I have been treated for EM, or I have been treated for neurologic?

DR. MEURICE: No.

CHAIR DAUM: Thank you. I have Ms. Fisher, Dr. Luft, and Dr. O'Fallen.

MS. FISHER: I just want to make sure I understand. Is it SmithKline Beecham's position that those who receive LYMErix vaccine, and then have symptoms of arthritis, myalgia, and other signs of deterioration in health following vaccination, and those who have had lyme disease, and those who have the DR4 allele, that they should be vaccinated with this vaccine?

DR. MEURICE: Yes.

DR. LUFT: Thank you.

CHAIR DAUM: Dr. Luft, please?

DR. LUFT: I just wanted to ask a question about the -- to go forward with the whole issue of whether these might be actual treatment failures.

It appears that from the data that you presented that there was no difference in the signs of symptoms in those patients who had, in other words, vaccine failure. And so that they probably -- do you have a serologic correlate of that?

And have you applied to see whether those patients

who develop the -- have you gone back to look at the original sera of those patients that go on to develop these treatment related, or whatever TRLA -- I don't even know what that is, treatment resistant, whether they had been vaccinated, and they did not have protective levels of antibody?

Do you understand what my question is?

DR. MEURICE: Well, I guess you are asking about the patients with difference in musculoskeletal symptoms, whether they had different titers than the subjects who did not develop those symptoms, is that what --

DR. LUFT: And especially in those who go on later to develop this, what is called TRLA, treatment resistant something.

DR. MEURICE: Well, as I said, we did not observe TRLA in this study. So we did have, as was mentioned, for the symptoms with early onset after vaccination, a higher proportion of vacinees who had musculoskeletal symptoms, than in the placebo group.

But for those system occurring late, that is more than 30 days after vaccination, there was no difference, be it in the duration, or the manifestations of the musculoskeletal symptoms, comparing the vacinees to the placebo.

DR. LUFT: And is there a good serologic correlation to protection?

DR. MEURICE: Well, we have made a proposal, and

this is under discussion with the Agency.

CHAIR DAUM: Dr. O'Fallen, please, and Dr. Kohl, and Dr. Kim.

DR. O'FALLEN: Somewhat related to Dr. Coyle's question. When was the self-reported lyme disease determined, was that prior to randomization?

DR. MEURICE: That was at study entry, as part of the medical history of each subject. So, yes, prior to randomization.

DR. O'FALLEN: You quoted arthritis rates and compared observed in the two groups. Did you compare those arthritis rates to expected rates from, say, population epidemiologic studies, or something like that?

DR. MEURICE: So your question is about the rates of arthritis in that study that are compared to what are the expected rates in the population?

DR. O'FALLEN: That is correct, you compared your treated groups, your treated and your placebo group, and I'm just asking if you compared either of those rates to that which would be expected in a normal population.

DR. MEURICE: Well, overall, if we look at all cases of arthritis, we had four percent of the subjects reporting arthritis, and that was 4.5 percent in the vacinees, and 4.1 percent in the placebos.

What we have looked at is the sex/gender

distribution for these cases, which was, if you look at a female to male sex ratio 4.8 to 1, whereas in the global population of the subjects, we have a global sex ratio of 0.7 to 1.

So a little bit more arthritis cases in the female population than in the male population, which is probably in accordance with the general population. But I don't have other rates.

DR. O'FALLEN: I guess I will take your answer as no.

CHAIR DAUM: Dr. Kohl, please.

DR. KOHL: I forgot my question.

CHAIR DAUM: Senior moment.

DR. KOHL: I'll come back.

CHAIR DAUM: We all have them, Steve. I don't want you to feel bad.

(Laughter.)

CHAIR DAUM: Dr. Kim, please.

DR. KIM: Your data was presented in terms of the incidence. Can you elaborate, or was there any information on the severity of the symptoms and signs?

DR. MEURICE: Yes. As I mentioned the severity was defined as interfering with daily life activities. And depending on the symptoms it was from zero to five percent, I think essentially five percent was observed for pain at the injection site.

And in general, I believe we can go back to the data, but it was two or three percent of serious cases in the musculoskeletal symptoms in general.

CHAIR DAUM: Thank you.

DR. MEURICE: That was similar in both placebo and vacinees.

CHAIR DAUM: Thank you. We will take a question now from Dr. Kohl. And then we will break for coffee.

DR. KOHL: This is for our experts. Do we have a handle on what the incidence of treatment resistant lyme arthritis is, and a good definition of that? After natural infection, of course.

CHAIR DAUM: Would one of the experts like to take that on? Dr. Dattwyler?

DR. DATTWYLER: I see a lot of patients, and I must say that treatment resistance lyme arthritis in our center is low, it is very rare. We see maybe one case a year.

And, you know, that is using very strict criteria, saying that the person had, you know, CDC criteria for sera positivity, good history, and usually is monoarticulate knee arthritis.

And under those circumstances we usually try to do synovial examinations, synovial fluid examinations, and then if possible synovial tissue biopsies, and try to PCR the organism.

And we have not been able to PCR the organism in

that type of arthritis, but we have found PCR positivity in the more classic lyme arthritis cases.

So I think there is a differential between the individual who has an infectious arthritis, and this other form of arthritis. And I think that is what Dr. Steere has pointed out. He has a larger interest in rheumologic cases than I do, and has a greater cohort of this type of patient. But I think it is similar.

CHAIR DAUM: Dr. Dattwyler, the number of one per year, of course, is helpful. It would be a little more helpful if you gave us some sense of how often you make diagnosis of lyme disease. This is one out of two, one out of 100, one out of 1,000?

DR. DATTWYLER: That come to our center?

CHAIR DAUM: Yes. You said you see this once a year.

DR. DATTWYLER: Well, first of all, the most people that come and think that have lyme disease don't have it. You are talking about -- we have similar experiences as everybody else, that only about ten to fifteen percent of the people presenting with what they feel is lyme disease really have it.

Under the -- to give you an example, and I think this is from Dr. Steere's work, he published a paper a number of years ago on arthritis from rheumatism comparing different oral regimens for lyme arthritis.

It took him, and this is -- had multiple practice sites in there, it appeared to take him about four years to acquire about 40 lyme arthritis patients for that study.

So I think the incidence of lyme arthritis, in general, has decreased markedly and concomitantly the incidence of treatment resistance has decreased.

The percent, I would say, is about 5, to 10, to 1 what we see. So for every person with this other phenomenon, whatever it is, versus infectious arthritis, you are talking about we see maybe 5 or 10 people with infectious arthritis for everybody.

And we are a referral center, so we are getting the tough cases.

CHAIR DAUM: Thank you very much. One final comment.

DR. LUFT: Just about that point. I don't think there is any real data. And I think it goes along with a lot of infectious diseases, or inflammatory diseases, in which there is no aetiology known, you know, whether you have an encephalitis, most of those you don't know what the aetiology is, maybe some of them can be one type of bacterium or another.

It is the same thing with arthritis. There are patients that come in and we don't have any ediology whether it turns out to be some organism or not, we don't know.

CHAIR DAUM: Thank you very much. It is coming up

on 10:40. We will break and resume at 10:55 exactly. Thank you.

(Whereupon, the above-entitled matter went off the record at 10:40 a.m. and went back on the record at 11:00 a.m.)

CHAIR DAUM: I hope we are feeling nourished and nurtured. I call the committee meeting back to order, please. And we will resume with the sponsor's presentation. Can we get everybody's attention, please, we are in session.

Dr. Bernard Hoet will be the next speaker on behalf of the sponsor.

DR. HOET: Good morning. As introduced by Dr. Kahn, I will review the post-licensure safety assessment, and I would like to address three following topics.

Next slide, please. So first I will present the post-licensure commitments, and leave the work to Dr. Platt, who will especially speak about the phase 4 study. And then I will present the findings of the passive post-marketing surveillance, and briefly afterwards, review the additional clinical trials, and especially the safety aspects of those, the types that have been performed since licensure of the vaccine.

At the moment of licensure we were performing the study on cellular immunity which was to be reported as post-licensure commitment. And this study has shown that there is no evidence of association between vaccination and the incidence of inflammatory arthropathy.

We were also requested to perform reproductive toxicity study in rats, which showed that there was no maternal or fetal toxicity in these animals.

We were requested to establish a pregnancy history, that has been established, and no unexpected findings have been reported to date.

And then a safety assessment cohort study has been set up by Dr. Richard Platt, who is professor at the Harvard Medical School. And I would like to ask him now, to come and present the status and the current results of his study.

DR. PLATT: Good morning. I appreciate the opportunity to discuss with you this work in progress, which we've been at for about two years.

The primary objective of this study is to evaluate whether exposure to lyme vaccine is a risk factor for new onset inflammatory arthropathy.

The secondary objectives are to evaluate whether exposure is a risk factor for a variety of other outcomes, including lyme disease, treatment resistant lyme disease rheumatoid arthritis, a variety of neurologic conditions, from allergic events, and death.

The study design is a prospective cohort study among HMO members who are immunized as part of their routine medical care. I should emphasize that there is no active recruitment for this study, we are merely observing the practice

as it is carried out among these HMO members.

The vacinees are identified through the automated claims data, and automated medical records of the managed care organization. We also identify a comparison group of non-recipients who are matched to the vaccine recipients by age, sex, and the medical practice where they receive their primary care.

And we perform passive and uniform surveillance which will last for at least four years that involves several steps. The first is screening of automated in-patient and out-patient claims for diagnosis which suggests outcomes of interest, followed by expert review of full text medical records for those who have suggested diagnosis. And, finally, we will link the entire cohort to the national death index.

Let me tell you, for a moment, why HMOs are good environments in which to do studies like these. But most important, I think, is that it provides an opportunity to observe the safety of vaccine in this case, under conditions of usual practice involving populations that aren't selected in any particular way.

HMOs have a considerable amount of information about their members, about the health care that they receive, and about their health status. And with effort it is possible to link those records together to obtain relatively complete and largely passive surveillance for outcomes of interest.

This passive surveillance has the advantage of

avoiding many of the kinds of bias that are problematic in other types of surveillance studies.

Because of this there are a number of epidemiologic studies that are grounded in HMOs. And I list here three examples of those. They are all ones in which this HMO, that is the home of this study is a participant.

They include the multicenter CDC vaccine safety data link study, the Centers for Education and Research and Therapeutics, that are sponsored by the Agency for Health Care Research and Quality, and FDA, and the NIH sponsored Cancer Research network.

The setting for the study has been the Harvard Pilgrim Health Care, which is a not-for-profit major teaching affiliate of Harvard Medical School.

The HMO is a joint sponsor with the medical school, the department of ambulatory care and prevention, which is responsible for the conduct of this study. All of the research conducted by this department is in the public domain.

Starting this year two additional HMOs will join the study. They are health partners in Minnesota, and a health plan in Massachusetts. We recruited these two additional sites because at the end of the first year it was clear that our recruitment was less than we had expected it to be.

And at the time that we did this solicitation these were the only HMOs of which I'm aware which were both capable of

participating, and willing to do this.

Let me tell you a little about the investigators. I'm the principal investigator, I'm a professor at Harvard Medical School, and the principal investigator for the Harvard Pilgrim site of this CDC vaccine safety data link. I'm also the principal investigator of an FDA cooperative agreement to study adverse drug effects.

And I'm the overall principal investigator for the HMO research network CERT. The co-investigators in this work include Dr. Arnold Chan, who is appointed at the school of public health in Harvard Medical School, and who is here today; Dr. Alexander Walker at the Harvard School of Public Health.

I would classify the three of us loosely as pharmaco-epidimiologists. Dr. Matthew Lang and Nancy Shadick of Harvard Medical School are rheumatologists who have interest in the epidemiology of lyme disease.

The rules and responsibilities for the study are listed here. We've developed this protocol in concert with the sponsor, with a considerable amount of input from FDA. The sponsor has been responsible for all of the interactions with FDA.

We investigators have complete responsibility for all of the research activities. That includes data gathering, data analysis, and report writing.

Finally we, we the investigators, own and control the data, have contractual authority to use the data as we see

fit, including publication when we think that is appropriate.

The time line for this study is shown here. As you know the vaccine was licensed at the beginning of 1999. We signed a contract to conduct the study in the spring of 1999, and the protocol was completed in the middle of 1999.

That protocol specified that new vacinees would be recruited for two years. We submitted an interim report in the middle of 2000 that listed the vacinees and all of their ICD-9 codes, including those both before and after they had received their first dose of lyme vaccine.

A second interim report added the control, or non-immunized individuals, and the third report submitted at the end of last year divided those ICD-9 codes into those that had been assigned, first assigned before immunization and those that were first assigned after immunization began.

The protocol was amended at the beginning of this year. A number of broader aims were added. And, in addition, the recruitment period was extended for another year.

As I mentioned to you, HMOs will join shortly. When they do, I should mention that when they do, all of their data, since the beginning of 1999 will become available.

Our next report will be due in March, and it will have the beginnings of the full text record reviews for individuals who have ICD-9 codes of interest. There will then be interim reports every six months until the study ends in 2005.

And in 2004 we will do the linkage to the National Death Index.

We characterize the vacinees in the following way. We identify them from automated claims files looking for CPT codes that -- the CPT code that indicates lyme vaccination.

We believe that this is a relatively complete ascertainment because the providers are only reimbursed for the cost of vaccine and immunization if they submit this code.

Among those for whom we find the code we restrict the population of those who are continuous HMO members since January of 1999. We identify all of their diagnosis code for the three years before vaccination, or for as long as they have been members if it is a shorter period than that.

And then for each of the interim reports that we submit we identify all of their interval immunizations and all of their new diagnosis codes assigned since the preceding report.

As I mentioned we do blinded review of the medical records that have codes of interest. The controls are identified in a three to one ratio for each vacinee.

We match on, as I mentioned, on practice, on gender, and on approximate age, using the same restrictions for continuous membership in the HMO.

We assign a referent date to each control since the vaccination date of the case to whom the individual is matched. And then we do exactly the same kind of case finding, by looking

for diagnosis codes before and after immunization, updating those for each interim report, and doing the blinded reviews.

We have determined that the immunization codes are highly accurate. A review of a random sample showed that 99 percent of the automated claims have supporting data in the clinician's full text record, indicating that the individuals were, in fact, immunized when the automated record says that they were.

And in addition we are confirming immunization status for all the records that are reviewed.

We confirm new events of interest by screening both in-patient and out-patient records for diagnosis codes, and then obtain the full text ambulatory record that matches that event.

There is a first level review by a chart extractor to eliminate events that clearly are not of interest, for instance, trauma, for instance clear statement that there is crystal arthropathy.

The charts for which there is no clear alternative explanation are reviewed by a rheumatologist, either Dr. Lang or Dr. Shadick, using a standardized abstraction form, and we are assessing the inter observer variability of our chart extractors.

Our analysis plan calls for us to compute incident rates and rate ratios to do that both accrued measure, and to stratify it by a number of potential risk factors. We intend to

asses the dose response relationship.

We will use multi-varied analysis principally proportional hazards, methods, but we will also use poisson regression to take into account any crossover of individuals who are initially assigned to the control population, and who subsequently become immunized.

And we will explore for unanticipated potential adverse effects by assessing the frequency with which codes are assigned to at least five individuals in the vaccine group.

The study size was set at 25,000 vaccinated, and 75,000 non-vaccinated individuals on the basis of two basic parameters. The first was an interest in finding approximately a two-fold excess risk of these conditions, and an assumption, or a guess, that the baseline rate would be approximately 2 per 10,000.

I have to tell you that there is no baseline data for this particular population. And so this was, we thought, a reasonable guess. But we are prepared to see either higher or lower incidence rate.

Our preliminary rates are these. Through the first half of 1999 about 2,500 individuals were immunized. Through the next year an additional 1,100 were immunized. The third interim report shows this 3,600 figure.

In our comparisons we compare to the 2,500, and we've done that because there is a reasonably long lag time in the

maturation of a claims data base before we are certain that it is complete.

And so we have held off on doing the comparative analysis for the additional 1,100 until we are satisfied that we have a complete claims data base.

About 2,800 of these individuals are recorded to have had two or more doses. These are the counts of the individuals who have had the assignment of one of the screening codes for a rheumatologic or musculoskeletal diagnosis that is first assigned after the first vaccine, or after the vaccine dose, or the referent day.

You can see that approximately 8 percent of both vacinees and comparators have had one of these codes assigned. We intentionally chose a broad array of codes to be potential indicators, because we wanted to be sensitive in our first round of identification of potential cases.

One estimate of potential severity is to look at individuals who are hospitalized with one of these new rheumatologic codes. And the results are shown here, it is one of the vacinees and seven of those in the comparison group for rates that are well under, for proportions that are well under one percent.

Let me emphasize that these medical records have not been reviewed yet, so these are numbers based just on assignment of diagnosis codes.

Our preliminary conclusions are these. First that, I believe, the premise is correct, that HMO based record linkage is able to identify vaccinees reliably, and that the first assignment of these diagnosis codes is approximately equally common in vacinees and in comparators.

Most of these don't represent outcomes of interest. It will be necessary for us to do the chart review to identify new onset codes of interest. We expect the first part of those chart reviews to be included in our fourth interim report, which is due in March, and to have the substantial bulk of the ones that we now know need to be reviewed, done by the time of our September report.

Our current plan is to continue the existing protocol and to bring these two new HMOs on line during this year. As I mentioned, all of their data, since the vaccine was introduced, will be available when that happens.

We don't know how many vacinees we will have recruited in the three HMOs by the end of this third year. It is possible that we won't have 25,000.

In that case I think that there are two strategies that could be considered. One is to use the data that we will have at the end of the third year to recompute the power and confidence limits, because by that time we will have substantial information on baseline, on the baseline rates of the events that we care about, and we will have a good idea of the sample size.

If we need to recruit additional subjects then, once again, there are two possibilities. One is to extend the recruitment period, the other would be to identify an additional HMO collaborator.

We will be entirely willing to do that. I do want to tell you, again, that we made a fairly thorough search for environments in which it would be possible to extend the recruitment.

And as of very recently there were no additional sites that appeared to be appropriate for that purpose. The sites that -- that is because one would need sites that are in endemic areas that are using the vaccine, and have a history of doing research like this, and are willing to commit their resources to the study.

And we have found no other potential collaborators at this moment. That may change in the next year, however.

That is where we stand now. I would be happy to answer questions either now or later, as you like.

CHAIR DAUM: I think we will take a few questions now.

Before we begin the questions, though, I would like to point out that this committee needs to be sure they deliberate the issues at hand in the best possible environment.

And therefore I would ask that people who have cell phones that keep going off, beepers that keep going off, please

turn them off now so that they don't continue to disrupt the proceedings.

We will now take committee questions. I have Ms. Fisher, Dr. Fagget, Dr. Manley, and Dr. Griffin, and Dr. Stephens. And, of course, our two consultants on the other side. I used to be able to remember ten things at once, and now it is more limited.

So we will just go, and we will get everybody to have a turn.

MS. FISHER: I assume there was exclusion criteria for those participating in the study. Did you include people who had had previous lyme disease, who had been vaccinated and had reactions, or would appear to be arthritis type reactions afterwards; did you exclude people who were sick at the time of vaccination; those with a history of autoimmune disorder in the family, what was your criteria?

DR. PLATT: Remember this is a passive study. That is we are reporting all of the vaccine experience of the -- so --

MS. FISHER: But you would have, I assume, for informed consent purposes, when you enroll people, and you did use -- at first you said that there was no active recruitment. And then later you said that there was recruitment.

And so you must have had some informed consent that was signed by those who were vaccinated. Was there an exclusion of certain categories of individuals?

DR. PLATT: I'm sorry if my second statement was misleading. There was no active recruitment, there was no special notification to providers, or to members of the HMO that there was any interest in doing a study.

So we are observing the use of vaccine as the several thousand providers, and million plus members of the HMO chose to use and receive it.

So the data I'm showing you are all of the experience. It will be possible, after the fact, to go back and comment on what proportion of the individuals who are immunized had a prior diagnosis of lyme disease, but they are all in the data that I'm showing you.

MS. FISHER: You have not answered my question.

DR. PLATT: I'm sorry about that.

MS. FISHER: About those who are vaccinated, was there an attempt to exclude certain categories of individuals? In other words, those who had a history of autoimmune disorders in the family, or personally; those who had had previous adverse reactions to perhaps other vaccines; those who were sick at the time of vaccination, etcetera?

DR. PLATT: Those decisions would have been made by the primary care practitioner who was caring for the individual. There was no study protocol that governed this. No one was immunized because of this study.

So my second use of the term recruitment was not

meant to indicate that there was any attempt to encourage individuals to be immunized. So there was no informed consent, because this was routine medical care that was delivered.

So if providers chose to exclude individuals on the basis of the criteria that you mentioned, then they would have done that, and we wouldn't see those people.

MS. FISHER: Absolutely affects the outcome of your study. It affects it because you don't understand what the history is. I mean, there had to have been some informed consent here in terms of which individuals were enrolled.

I would think that before vaccination took place the individuals would have to --

CHAIR DAUM: Ms. Fisher, I think the question has been asked and answered, there was not informed consent. And whether there should have been, or could have been, would have been, is something the committee is welcome to discuss.

DR. GRIFFIN: This is a licensed vaccine, it doesn't require informed consent for a licensed vaccine, right?

CHAIR DAUM: I am not sure that is a correct view. But the point is that there wasn't. Dr. Fagget, please.

DR. FAGGET: Dr. Platt, had you finished your answer?

DR. PLATT: I'm sorry?

DR. FAGGET: Had you finished?

DR. PLATT: Yes.

DR. FAGGET: My question is relative to underreporting. As a former HMO medical director I'm well aware that a five to seven minute visit does not give, really, time in many cases, for that primary care physician to really pick up subclinical arthritic conditions, and things like that.

Also you have already mentioned that claims data is definitely require medical record review in order to verify.

DR. PLATT: Yes.

DR. FAGGET: So my question is, do you have a feel for how much time your HMO practitioner has to spend on each patient, and are you comfortable that in this -- yes, HMOs are a good source, but is the visit adequate to give you what you need in terms of a really comprehensive ICD-9 diagnosis?

DR. PLATT: I'm sure the HMO would tell you that there is ample time for a thorough evaluation. But I take your point that claims data do not provide the same depth of information as a structured interview does. We just have to understand that.

So the evidence that I can bring to you are two pieces. One is, in the follow-up interval that has been available, eight percent of vacinees have had a new diagnosis of a code that we consider to be an indicator code.

So there are lots of people who have codes assigned. And the second is I think that to the extent that conditions are severe ones, they are likely to be more reliably

captured.

DR. FAGGET: Will you breakout the category of primary care provider, nurse practitioner versus physician, versus PA, will you have that information?

DR. PLATT: I don't have it now, I will have to check on whether we can find it for you.

DR. FAGGET: This is preliminary, right, what you are reporting today is preliminary?

DR. PLATT: This is the first two years of a seven year proposition.

CHAIR DAUM: I have Dr. Manley, Stephens, Goldberg and Davis. Dr. Manley, please.

DR. MANLEY: Thank you. My question is related to one of the earlier questions. You've explained about the fact that this was not a proactive study, there was no enrollment, though you did use the word recruitment several times.

But I'm wondering about the pregnancy registry. You stated there is no evidence, to date. What can you tell us about the pregnancy registry, are there patients that have been assigned to that registry, are there numbers, any information at all on where we are?

DR. PLATT: Right. This study is not linked to that pregnancy registry, so I would look to one of the sponsors.

DR. MANLEY: But the data you are collecting so far, at the HMO, if a pregnant woman did receive immunization

would you be able to tell us, at this point, that that had happened, and how many times it might have happened?

DR. PLATT: It is knowable, we haven't done that yet.

CHAIR DAUM: Okay. Dr. Stephens?

DR. STEPHENS: I think this is an important study and hopefully we will learn some very valuable lessons. My questions concern enrollment, and the lower than expected rate of enrollment.

Can you comment on why you think that is, is that imply because the vaccine is not being given, or is it a reporting issue of individuals being vaccinated?

And the requirement for continuous participation of the HMO, do you have drop out factor excluding from the study?

DR. PLATT: I'm fairly confident that the reason is because the vaccine hasn't been -- I'm reasonably confident that we are finding the vaccine that has been given in the HMO.

And the, as I said, we are observing what clinicians and patients decide to use. The vaccine is what the HMO calls a covered benefit, so there is no economic disincentive to use the vaccine.

I do not think that we have been losing individuals because of enrollment issues. That is, most of the -- there is attrition in membership, but we are following individuals until the time that they disenroll.

So disenrollment wouldn't eliminate anyone, because we would merely censor their observation.

CHAIR DAUM: Can you give us just a sense of turnover of your HMO population?

DR. PLATT: Our HDAS figure is 14 percent.

CHAIR DAUM: Per year?

DR. PLATT: Yes.

CHAIR DAUM: Dr. Goldberg, please.

DR. GOLDBERG: A couple of questions, and some of this follows on what Dr. Fagget asked before. You are reviewing only the codes of interest in these reviews.

Have you done any sampling, or have you any procedures to review, other records that aren't among vacinees in controls that don't show these codes of interest to see what the underreporting might be?

And to follow on that, have you trained or informed all of the physicians who see these patients in what you are looking for, in a more active way, even though the patient aspect of it is passive?

And then thirdly, do you have a data safety monitor in process that is organized and doing the blinded review, and then summarizing the data in some preplanned way?

DR. PLATT: I'm old enough that three things is going to be hard to keep in mind.

DR. GOLDBERG: You can take them one at a time.

DR. PLATT: We are reviewing only records that have a code of interest. We develop, I think by a consensus process, a very broad list of codes that includes things that we didn't really believe that clinicians would assign if an individual had an outcome of interest.

And in choosing that very broad list of codes we made a decision that the yield in the group that weren't included would likely be low enough that it would not be a fruitful search.

We are entirely open to other kinds of sampling. But we have to be careful about making decisions about how to do that sampling in an informative way.

Because if we think of the background occurrence rate is 1 in a 1,000, and people who don't have one of those codes, then we would have to review several thousand charts to find one.

So the second question was, how did we -- what did we -- how did we inform the clinicians. And we didn't inform the clinicians. That was a design feature of the study to, in large measure, to avoid potential reporting biases to look at the diagnoses that clinicians chose to assign as part of their routine medical care.

And, finally, we have a -- if I understand your third question properly, we have a very well specified process for the reviewing of the charts, and the recording of the events that we find.

That has been -- was that your third question?

DR. GOLDBERG: That was part of it. The other part was, is this being reviewed on a routine basis, you know, in some format that one can see the changes over time?

DR. PLATT: Right. Our periodic reports, which have been quarterly and now are every six months, each include a sort of a full update. So it is both incremental data and cumulative results.

So each of those reports there is an opportunity to do that comparison.

DR. GOLDBERG: Can I just ask one follow on question? On the -- you said that you are not required, you haven't trained the physicians to really asses this.

Do you have some idea of how physicians do report, how many diagnoses do they report at a given time, is it related to the severity? If the patient has a severe illness of another kind, and then they also are complaining about these lyme symptoms, or whatever, would that be recorded?

And do you have any substudies to asses this sort of thing, so that you could characterize your reporting mechanisms?

DR. PLATT: It is the nature of these claims files that they can report up to three diagnosis at a visit.

CHAIR DAUM: I have Dr. Davis, Griffin, and Luft. Dr. Davis?

DR. DAVIS: Thank you. My question has to do with the consistency of using codes, since you are going to be bringing on two more HMOs. Do you have a method of assessing the consistency of the use of codes across the HMOs?

DR. PLATT: We can look at the frequency distribution of use of codes and stratify that by age and sex, that would give us the best sense of that.

We have done several other collaborative studies with these HMOs, and have found it could be, the data to be reasonably homogenous across the HMOs for the kinds of exposure outcomes that have been of interest in other pharmacoepidimiology studies.

CHAIR DAUM: Dr. Griffin, please.

DR. GRIFFIN: I am really following up on the question that Dr. Stephens asked, because I'm interested in the enrollment problems, and how much that is going to continue to hinder this study.

Because I think it is really an important study to get the kind of information that the committee, and probably everybody else is interested in.

So you had many fewer patients that enrolled sort of in the second, or two six months than you did in the first six months, which is maybe what you would expect with a new vaccine, you have sort of a buildup of people who wanted it.

So I have two questions. One is, is there any just

sort of general idea of why the vaccine has had a much lower uptake than one would have, perhaps, what you anticipated, obviously in this HMO.

And, second, is there any idea, ballpark idea, of how many doses have been given in the two other HMOs that you are bringing on line?

DR. PLATT: I honestly don't have an expert explanation for the rate of use of the vaccine. The other two HMOs, when we have the data from those other two HMOs, we expect to have between two and three times the total that we have now.

Which would mean a total of somewhere between 7,000 and 9,000 through two years of follow up.

DR. GRIFFIN: There is probably no reason to think in the third year that that will dramatically increase in frequency, that there will be an incremental additive number of individuals. It sounds like you are going to have a hard time getting 25,000, I guess.

DR. PLATT: We can predict equally well. There is really no information on that.

CHAIR DAUM: I have Dr. Luft, Dr. Kohl, Dr. O'Fallen. Dr. Luft, please.

DR. LUFT: Conceptually I love this approach because it uses computers, it is a lot of data that you can go through.

But I think one of the issues, you know, coming

from the point of view of the department chair of ICB-9 codes as to what is the purpose of those codes from the physician's point of view, and that is for billing.

This is the way, and what you do is you try to -- you look at diagnosis and you put in as complex of the issues as possible in order to be able to get as high of a level of care, and that is the incentive.

So the incentive from the physician's point of view is a financial thing that they have to represent, it is not to look for subtleties.

And I think that there may be a problem in what your readout is, as a result of that, especially you try to get three diagnosis. If I have someone who comes in with congestive heart failure, renal disease, diabetes, and joint pain, you will see where the first three, the complex disease will be first, and then joint pain will, myalgia or whatever, won't ever make it up there.

The other thing that most of these -- because I'm constantly dealing with my docs regarding billing to get them to fill out their billing sheets, is that they do what is easiest.

They are not going to look at the long list, they do what they have some facility at knowing. So, for instance, if they single out hypertensives, etcetera, and they could quickly write down those ICD-9 codes, they just do that.

It is not even that they will go in and look for

the subtle diagnosis, or the things that are out of -- and I think those are two, you know, I'm just kind of -- in some ways I just love this stuff, because it is just, like I said, it is reams of data, and you are able to compare it.

But I'm not sure what the acquisition of the data is as accurate as you want. And that is basically it.

CHAIR DAUM: Thank you.

DR. PLATT: I agree with all of the above, and that is why I would never publish a result, or suggest to the committee that it make conclusions on the basis of ICD-9 codes alone.

We use the ICD-9 codes as a very rough strainer to find the records. Among the thousands of people who are participants in the study, we need to find the hundreds whose charts need to be reviewed. And that is the purpose of using the ICD-9 codes.

And we trust the clinicians to get at least the right body system, organ system in their diagnosis codes. And if they don't do that then we will have missed these outcomes.

CHAIR DAUM: We are going to take questions or comments from Drs. Kohl, O'Fallen, and Diaz, and then we are going to ask Dr. Kahn to wrap up the sponsor's presentation. Dr. Kohl?

DR. KOHL: I took my Ginko Balboa so that I can't remember my questions. I have two questions.

CHAIR DAUM: I was going to make a comment, and I decided that we have been friends for a long time.

DR. KOHL: In the summary we received as handout material labeled Synopsis of LYMErix Phase IV Observational Study, it states: While no obvious patterns are present, and I'm paraphrasing here, data suggests a higher incidence of rheumanological conditions among vacinees than non-vaccinees.

Was that referring to the 8.5 versus 7.5 percent, or are there other higher --

DR. PLATT: I'm sorry, I don't know. I'm aware of no other data that suggests that there is a higher rate of assignment of these codes.

DR. KOHL: Because you said they were similar, about 8 percent, and the handout says there is a higher --

DR. PLATT: One is eight and a half percent and the other is, I think, 7.8 percent.

DR. KOHL: Okay, and that is what you are referring to, okay. Because you modified your conclusion a little bit.

The second question gets back to what I think is a concern among committee members. And I'm going to push you a little harder, and that is recruitment of vacinees.

It seems very slow, and if what Dr. Griffin said is true, it seems that possibly there was a bulk of people who wanted a vaccine, and now there is a fall off, although it is possible there were documents who didn't want to use the new vaccine to begin with, and now there will be an increased utilization as they feel more comfortable.

And it is possible that a hearing like this will make people less comfortable, and docs less comfortable, and there will be a gigantic fall off.

Do you have any idea what is going on? Because I'm concerned, where a year and a half or so, post-licensure, having mandated this kind of study, and it doesn't look like we are getting it very quickly.

And if there is a real problem out there, this is a question that needs to be answered with some timeliness. So give us a feeling for how quickly this is going.

DR. PLATT: I can't give you a sense of what the recruitment will be. I do think that by the end of this year, with the addition of the data from the new HMOs, we will likely be at two to three times the number of individuals, and at that point my view is we will have real information about the relative risk of these outcomes.

The tyranny of power calculations is such that very large increases of numbers buy you a relatively small increase in precision. So a study that is half the size, in fact, will have pretty good power to exclude a relative risk of three, as opposed to a relative risk of two that we are talking about.

I'm not suggesting that the study be scaled back. But, in fact, even though -- I won't use the word recruitment, is slower than we expected, in fact there will be substantial information available, I think, by the end of the year.

DR. KOHL: But we have been told, so far, that this is a very rare condition. So rare that we don't even have an incidence number for treatment resistant lyme arthritis. And I'm concerned that the study is not going to be powerful enough, maybe even at 25,000, but if you scale it back further, that is a real concern.

CHAIR DAUM: Dr. Kohl, what I think we should do here is not push Dr. Platt further on this point, but rather raise this important issue when we have more general discussion with the sponsor, and with our FDA colleagues, because they have a lot of input as to how the study is conducted.

And Dr. Platt may have a limit to what he can accomplish within the context of his one, two, or even three HMOs in terms of enrollment.

And I'm going to suggest that we use the word enrollment rather than recruitment, because I think we are getting some unnecessary juice here in response to the word recruitment.

Enrollment is what you are doing, really, at least as I understand it.

We had Dr. O'Fallen, and Dr. Diaz. And then we will move on.

DR. O'FALLEN: My primary point was very eloquently expressed by Dr. Kohl. I think we have a serious problem of enrollment. And I agree that is the proper word.

You all anticipated, obviously, 25,000 in two

years. You are optimistically telling us that the addition of, let's pick on Minnesota, where the disease is not as endemic as it is in Massachusetts, I can't believe that the enrollment is likely to be as big there as you are anticipating, either.

And then we have the potential bias, if you can only list three ICD-8 codes that the doctors who gave the vaccine will be more likely to list those codes, than we will find in the controls.

And so we will have to be trying to sort a lot of that out, too. So I'm seriously concerned about the study as well.

CHAIR DAUM: Thank you. Dr. Diaz, please.

DR. DIAZ: I think I'm the third or fourth in line with very similar question, and it has to do with this question about enrollment. And this question could be answered now, or later during the discussion.

But I think if the study is designed to look at safety as it is used in the general population, then we will, at some point, need to have some information about what the practices are of physicians who are giving the vaccine to these individuals, ie, are they offering the vaccine to everyone equally, or are they selectively offering the vaccine based upon subsets of patients and concerns about safety issues?

CHAIR DAUM: Do you want to respond to that? Or I think you already have.

DR. DIAZ: I'm curious if anyone has -- I guess the question is, then, does anyone, either you or the sponsor, have information about physician practices with this vaccine, currently?

DR. PLATT: There are, so far, there are approximately 250 practices that have immunized someone who is included in the results that I've shown you. And they have, we guess, a couple of thousand providers.

The HMO communicates to those providers in a very general sort of way, providing the CDC guidelines for use of vaccine. That is the information that has officially moved back and forth in this provider group.

CHAIR DAUM: Thank you very much, Dr. Platt.

Now, can I get a sense, from the sponsor, of how much more time they need? I thought we were down to our final speaker. How long does Dr. Hoet need?

DR. HOET: I have seven slides, and then there will --

CHAIR DAUM: I think we can handle that. Let's go as quickly as we can through this, if you would, please.

DR. HOET: Thank you. Thank you, Dr. Platt.

The vaccine is now on the market since two years, and 1.4 million doses have been distributed. And to date 984 adverse events have been reported to the company, until November 30th.

And what has been observed is that the only reactogenicity profile that had been reported during the clinical development, and that is presenting information of LYMErix occurred to -- it is confirmed.

And that some of the symptoms that are reported in prescribing information of LYMErix appear to occur concomitantly with an early onset after vaccination. Also hypersensitivity have been reported very rarely.

The slide here compares the adverse event reported during the post-marketing surveillance with the adverse events that were reported during the clinical development.

And in the left column here you see the adverse events that have been reported during the efficacy study to occur statistically significantly more frequently in the vaccinated group, as compared to the placebo group.

And on the right side you see the ten most frequently reported adverse event in the passive post-marketing report. And these adverse events reported through the post-marketing surveillance are very similar to those reported on the label.

Next slide, please. In view of the theoretical concern faced regarding the risk of inducing autoimmune arthritis after lyme disease, all the cases of arthritis or rheumatoid arthritis have been analyzed.

And up to September 25th of last year 70 cases have

been reported. And an in-depth review of the data show that there is no evidence that incidence is higher than in the general population, no practical or clinical pattern was identified, and no clustering time to onset was observed.

We do not consider that the arthritis cases reported in the post-marketing surveillance are associated with vaccination. However, as part of our continuing effort to address the theoretical concerns, we are convening a panel of experts to independently review this data. And this is ongoing.

Now, since licensure of the vaccine several clinical studies have been performed, or initiated. Firstly in the older population where cohorts of the efficacy study have been followed up, and secondly in the pediatric population.

And I will now give you the available safety data of these studies. In the blue box here you see the results that were available at the moment of licensure. First you have the Lyme-008 efficacy study that enrolled 10,936 individuals randomly allocated to placebo or vaccine.

And that lasted with a follow up of 20 months. This study, as explained earlier, was followed up by a safety follow-up of four months, and these are the data that are available in the file.

And then most of the vacinees of this study have been participating to a long-term follow-up for an additional year, and this is approximately 5,000 subjects, and 352 have

participated to booster studies.

The majority of the placebo cohorts has also been included in further clinical studies, and have received the vaccine.

Approximately 4,400 out of them have received the vaccine according to the license schedule. And somewhat less than 1,000, according to alternative schedules.

And 550, 1,550 of those subjects have participated to further booster studies. Out of the 4,400 subjects having received the vaccine, according to the license schedule, 3, 578 participated to a crossover part of the efficacy study, for which I will show you preliminary results in a moment.

Next slide. So this was an open label study with crossover vaccination of the placebo recipients of the Lyme-008. 3,578 subjects, the schedule was the one that is licensed for the moment.

And there was an unsolicited adverse event reporting by a safety postcard. Similar to the pivotal efficacy study the most frequently reported adverse events were injection site pain, myalgia, arthralgia, and influenza like symptoms.

So two alternative schedules have been studied, namely 0, 1, and 6 months that was compared to the classical 1, 1, 12 months in 400 subjects per group, and the 0, 1, 2 plus 12 months, versus a 0, 1, 12 month in 500 subjects.

In addition, approximately 3,800 subjects

participated to booster studies, receiving up to six doses of vaccine in total. Regarding the pediatric population 4,000 subjects age 4 to 18 years participated in these studies, out of which 3,000 received LYMErix according to the 0, 1, 12 month schedule.

In all those studies the nature and the frequency of the adverse events were similar to the pre-licensure clinical trial experience.

In addition to the more than 6,000 subjects that have been vaccinated before licensure of the vaccine, more than 8,000 subjects have received a vaccine in the course of clinical studies since licensure.

And so safety data has been collected, in controlled settings, on more than 14, 000 vacinees to which the number of the cohort studies can be added.

In conclusion of regarding the licensure commitments, the post-licensure commitments, the study on cellular immunity showed no evidence of association between vaccination and incidence of inflammatory arthropathy, no maternal or fetal reproductive toxicity was seen in rats, and the pregnancy registry has been established, and no unexpected observations were made.

And the cohort study to asses the safety of LYMErix show enrollment lower than expected due to the low vaccination rates of the search population. No difference was, however, observed in the event codes between vacinees and the control

group.

The post-marketing data have shown that the most frequently reported adverse events involved reactogenicity with symptoms already described in the product label.

These symptoms, these reports show that in certain individuals these symptoms are described as occurring concomitantly. Hypersensitivity has been reported very rarely in post-marketing surveillance, and the arthritis cases observed in the post-marketing surveillance are not considered to be associated with vaccination.

Clinical studies involving more than 8,000 vacinees confirm that the safety profile observed during the development of the vaccine is --

CHAIR DAUM: Thank you, Dr. Hoet.

DR. HOET: And now I will --

CHAIR DAUM: I think I will now ask Dr. Kahn to show her conclusion slide, and then I will take Dr. Hoet and Kahn's presentation together for a few questions.

DR. KAHN: Thank you. Just one conclusion slide, an overall conclusion.

In conclusion now we have shown you safety experience in excess of 18,000 subjects in a number of controlled settings. Again, 1.4 million doses have been distributed in the marketplace.

All of the data accrued since licensure concern the

safety of profile defined at the time of licensure, and in particular we should confirm here that there were no cases of TRLA in any of our control trials extensions or, indeed, in the post-marketing surveillance.

As for all vaccines GSK is committed to continuing the safety assessment in collaboration with the agency.

Thank you, that is the end of GSK.

CHAIR DAUM: Thank you to the sponsors for their presentation.

We have time for a couple of questions on Dr. Hoet and Dr. Kahn's last comments. Dr. Kohl, Dr. Griffin.

DR. KOHL: I appreciate the presentation by the manufacturers. I'm sure, due to shortage of time, we could not see specific data on some of the last studies presented.

My question is, does the FDA have that data for the post-licensure studies, in order to be able to scrutinize the specific side effects of the vaccine?

DR. KAHN: For many of these downstream indications, where we have clinical trials, there are supplements, indeed, under review. And for that reason we can allude to the them because we have the empirical safety data to look at, but we can't really comment specifically, because they are -- it would be unwarranted at this time, otherwise.

DR. KOHL: Under review in the company, or under review at the FDA?

DR. KAHN: At the FDA.

CHAIR DAUM: Dr. Griffin, please.

DR. GRIFFIN: That may be the answer to my question, too, because I was wondering what you meant by hypersensitivity. If this is an immediate hypersensitivity, sort of a delayed type hypersensitivity, or --

CHAIR DAUM: Dr. Stephens, then Dr. Coyle, then -- I'm sorry.

DR. HOET: In the post-marketing settings some immediate hypersensitivity has been observed.

CHAIR DAUM: Thank you. Dr. Stephens?

DR. STEPHENS: Do you have experience with this, or related vaccine, in Europe?

DR. HOET: Well, we are currently working in analyzing the possibilities of developing lyme vaccines in Europe, also.

DR. STEPHENS: Do you have clinical trials ongoing in Europe?

DR. HOET: There are phase II trials ongoing in Europe at the moment.

DR. STEPHENS: Phase II trials.

CHAIR DAUM: Dr. Estes, please.

DR. ESTES: You summarized that you had studies on cellular immunity, where there was no evidence of an association between vaccination and inflammatory reactions.

Did you show us that data, the cellular immunity studies? Because my recollection was that the summary from the FDA is that that data was limited, and that final conclusions could not be made.

Am I correct in that?

DR. KAHN: Perhaps I can call on Dr. Montagne to answer that question.

DR. MONTAGNE: Well, actually I'm from R&D, I'm not sure it is needed to go into the details of the data. But indeed, as has been presented by the FDA this morning, indeed this is a primary report, for which the first purpose was to see if there was some sort of to different peptides, to the OspA and to the different peptides.

And we can't conclude, because of the background, to any significant, both hemologically and statistically significant difference. However, what we just can see is that there is some lympho proliferation against some peptides.

And, for example, we confirm that, indeed, some TDR4 allele are used to present some peptide, as expected, just as expected. I don't know if you want to see the real data.

DR. ESTES: I think that is okay, I just wanted to confirm that the conclusions that we heard from the FDA this morning, that the study was limited, was a little different than the conclusion on your slide.

DR. MONTAGNE: On top of that, on top of the

immunological data, what is true is that there was no correlation between the clinical picture and those data. So those data are confirmed how some peptides can induce some proliferation in association with some DR allele, and especially with DR4.

But what is interesting is that, indeed, there was no correlation between these data, this lympho proliferation in individual patients, and some clinical picture.

CHAIR DAUM: Dr. Coyle, did you have your hand up before? Dr. Coyle, then Dr. O' Fallen, and then we need to move on.

DR. COYLE: I wanted to ask you about the concomitant symptoms that have been identified post-marketing, which I think in the report have been about 183 patients, which would be about 20 percent.

Do you have, is there any data of those 183 or so, how long the symptoms are lasting? Because there was a comment on months, and months, and months.

Is there any data on those concomitant symptom group?

DR. HOET: Well, this is post-marketing data that have, effectively, elements on the post-marketing duration for certain of these symptoms.

The best way to analyze this data, the post-marketing setting, is -- the best way to analyze this long-term follow-up, it is always difficult, in post-marketing settings to

have this follow-up, and to look at them.

So it is a good practice to go back to more standardized and controlled elements. And what we have been doing is looking back to these kinds of symptoms into the efficacy study. And when we have been doing such an analysis we have been found that a certain percentage of subjects effectively have long-term, long-lasting adverse event in the vaccine group.

But this was not statistically different from the placebo group. And so, effectively, some of these adverse events that have been reported, either in the post-marketing surveillance, or in the clinical studies, last for a long time, but this is not longer than what is observed in the placebo group of the efficacy study.

CHAIR DAUM: We are going to take two more questions. Dr. O'Fallen, please, I'm sorry for butchering your name before.

DR. O'FALLEN: It is not the first time.

The pregnancy registry, and the comments that I've heard really disturb me. You've made it sound as though you find no consequences, and yet you summarize, in one situation, that you know the outcomes of only 13 of 30 pregnancies, and in 4 of those 13 pregnancies the outcome was an abortion.

I don't consider that to be showing no pattern of anything. I think you have very little data and those kinds of statements I think should be made much more reluctantly than you

seem to be making them.

DR. WHEADON: I'm David Wheadon, Vice President of Regulatory Affairs at Glaxo Smith Kline. A pregnancy registry is certainly one of the things we standardly do with any newly introduced drug or vaccine.

I think the statement is that to date, in terms of the pregnancies that have been reported to us, we've not seen anything that is unexpected.

So certainly spontaneous abortion, within the context of pregnancy, in an overall population, is not something that is unexpected. And I think that was, indeed, what was intended to be said by the conclusionary statement.

CHAIR DAUM: Do you want to follow up, briefly, very briefly?

DR. O'FALLEN: What is unexpected is the rate of abortions, 4 out of 13.

CHAIR DAUM: Dr. Ferrieri, please, and then we will move on.

DR. FERRIERI: Dr. Kahn, could you clarify for me if you have revised the package inserts since licensure, the language of change in the package insert, and the information prompting any changes, if such changes took place?

DR. KAHN: At this time we've just seen a review of the post-marketing experience. And the two categories that Dr. Hoet discussed.

I think what we are talking about, first and foremost, we have discussed with the FDA the possibility of this, there has been no submission on this, so we are not even at the point of saying that one is warranted.

But certainly the post-marketing experience has allowed us to better describe or characterize the early onset, the early reactogenicity in terms of their concomitant reporting.

But I don't think we see it as different from what was reported in the package insert to date. The hypersensitivity reactions is another issue that we will be discussing.

CHAIR DAUM: Thank you very much. We will now conclude the sponsor's presentation, and move back to additional presentation from the FDA.

Before we call on Dr. Robert Ball, I would like to ask Dr. Karen Elkins to come up, who had a couple of remarks for us, that sounded like they might clarify some earlier confusion.

And once Dr. Elkins is done -- that would be fine, they will turn it around for you.

DR. ELKINS: Just to offer a few clarifications in return to the questions that were rattling around on the subject of animal models.

There is a long history of using both mice, hamsters, and dogs as animal models for lyme disease, and perhaps others that are familiar with this literature might want to comment as well.

In regards to the C3H HEGJ mice inbred strains of mice were surveyed about a decade ago, in a systematic way, by several investigators, including Eulick Shadley and Max Simon in Germany, with the finding that HEJs appear to be unusually susceptible to the development of arthritis after infection with borrelia.

There was some hint that there was an association with the H2 type of the mice, but there are certainly examples in which mice having the same HL, or H2 alleles, as HEJs, were not particularly susceptible to the development of arthritis.

They have been studied extensively for the pathogenesis, and I think it is fair to say that the mechanism of development of that arthritis is not well understood, there has been data presented that that suggests that it could be related to the development of both CD4 and CD8 positive t-cells that recognize OspA.

But it is, at this time, I think, an open question. The -- with regard to the question of whether vaccination with OspA has been studied in mice, instead of the HEJ model, I think this has been best examined in transgenic mice, in which the HLA 0401 allele, I believe, was introduced as a transgene into mice.

And I think that it was initially on the 129 background, and then those were back-crossed on the B10s. And those were intended to be the model, if you will, for genetic control of development of arthritis in animals.

However, when those transgenic mice were infected, they did not develop fulminate arthritis, as I understand it. So that model has not been pursued, and I'm not aware of studies using recombinant OspA, or any recombinant proteins that have been studied in those mice, or at least reported publicly.

Now, the hamsters have also been used to study the development of arthritis following fulminate disease, and there has been one study reported looking at vaccination with recombinant OspA followed by infection.

And I believe that speaks to Dr. Griffin's question. These were an inbred strain of hamsters that I believe are LSH hamsters, and I know absolutely nothing about the HLA types of a relationship between the HLA types in the hamsters, and in humans.

But these hamsters, also, are fairly susceptible to the development of arthritis after infection alone.

One study from Ron Schmells in Wisconsin vaccinated mice with, I believe, 30, 60, or 120 micrograms of recombinant OspA, this was a home brew preparation of recombinant OspA that was absorbed to alum, but it was not the LYMErix product.

And the group reported that mice that were vaccinated with OspA did not get any observable hind paw swelling. But that when challenged with borrelia, 11 or 12 days, I believe, after vaccination, there was an increase in hind paw swelling, compared to those that were only challenged and not vaccinated.

There were a couple of features of that particular set of experiments that may or may not be relevant to the vaccination situation. First the time interval between vaccination and challenge with borrelia was very short, either 11 or 12 days.

There was sub-dose response data presented. The 120 microgram dose, I believe, showed less change with challenge than the 30 or the 60 microgram dose, which was a little peculiar.

And the other way around, that is, challenge followed by vaccination with purified protein was not reported.

CHAIR DAUM: Thank you, Dr. Elkins. Will you be around later in case people want to question you further about that?

We will now introduce Dr. Ball to give us a report on the VAERS data from the FDA.

DR. BALL: Good afternoon. Today I will be speaking about adverse events reported to VAERS following LYMErix, and then briefly discuss our plans for follow-up studies to evaluate the safety to the vaccine.

Before I get into the details of the adverse events reported after LYMErix, I would like to give a brief introduction to the vaccine adverse event reporting system.

It is a national system for surveillance of adverse events after vaccination, and it receives about 11,000 reports per year. It is jointly managed by the FDA and the CDC.

Reports are received from health professionals, vaccine manufacturers, and the public. Anyone can submit a report about any event, and all reports are accepted into the data base.

This effort to cast a wide net results in both causal and coincidental events being captured. All death and serious reports, which are defined as events requiring hospitalization, prolongation of hospitalization, life-threatening illness, or permanent disability as defined by the reporter, receive follow-up to obtain missing information, and when possible, detailed medical records.

Death and serious reports are reviewed by FDA medical officers upon receipt. VAERS is used to detect unrecognized adverse events, to monitor reactions, to identify possible risk factors for adverse events, and to conduct vaccine lot surveillance.

Surveillance systems such as VAERS are subject to many limitations. They include the fact that reported diagnosis are not verified if medical records are not included, or obtained in the follow-up.

There is lack of consistent diagnostic criteria applied to the reports. Reports are coded using a system called COSTART, which I will describe in a little more detail later.

There is a wide range in data quality. The reports range from brief descriptions to complete medical records. There is underreporting, although the amount of underreporting is

unknown.

There is inadequate denominator data. We have information on doses distributed, not doses administered, and there is no data on the demographics of vaccine recipients, in particular, age or gender.

And there is also no unvaccinated control group. So as a result it is usually not possible to asses whether a vaccine caused the reported adverse event.

I just want to show you the VAERS form, and I've highlighted the block 7. This is the block that is available for reports to describe events, and oftentimes this is the only information that we receive from reporters.

So given the limitations of VAERS, how do we use the system? We use it by describing characteristics, and looking for patterns to detect signals of adverse events that could be plausibly linked to a vaccine.

We do this by looking for unusual clustering by age, gender, time-to-onset, or dose. We examine positive rechallenge reports, which are defined as reports in an event after one dose, with the same event following subsequent doses.

And then we also examine symptom codes and clinical characteristics for unique or unusual patterns. We also evaluate the biological plausibility of a vaccine adverse event relationship, look at pre-existing conditions, and concomitant illness and medication use that can also influence the adverse

event.

But signals detected through the analysis of VAERS data almost always require confirmation through another type of study.

As I mentioned, there are no standardized case definitions in VAERS. And we use a system known as COSTART. We rely on coding of reports by non-physician nosologists using the system.

Within COSTART coding depends on the use of certain words or phrases in a report. For example, a report would be coded rheumatoid arthritis, and simply if that diagnosis is mentioned in the report without confirmation.

The report might be coded arthritis, if the report mentions the word arthritis, or arthritic, and a report would be coded as arthrosis if the report mentions joint swelling.

As a result, reports with different degrees of diagnostic precision may have the same coding term. And coding terms must be interpreted very cautiously.

I will shift gears to reviewing the adverse events reported after LYMErix. Again, the purpose is to describe the characteristics and look for patterns to detect events that could be plausibly linked to the vaccine.

We reviewed all reports from December 21st, 1998, which is the date of licensure, through October 31st, 2000.

And I'm going to describe, today, selected adverse

events, including the death and serious reports, hypersensitivity reports, because they are known to occur after many vaccines, reports of facial paralysis, and reports coded arthritis, or arthrosis, rheumatoid arthritis, because of the association between arthritis and lyme disease, and facial paralysis and lyme disease. Also reports mentioning lyme disease.

I am also going to discuss selected potential risk factors, including self-reported HLA types, and self reported history of lyme disease, because of the theoretical concerns of increased susceptibility to arthritis in these groups.

So from December '98 through October 31st, 2000, there were 1,048 reports in VAERS with approximately 1.4 million doses distributed. The vast majority of those reports occurred after lyme vaccine alone, there were no other simultaneously administered vaccines.

There were four deaths reported to VAERS, 85 serious reports, which were defined as hospitalization, prolongation of hospitalization, disability, or a life-threatening illness as defined by the reporter.

And of the selected adverse events there were 22 reports of hypersensitivity specifically urticaria, or urticaria with respiratory symptoms. There were 133 arthritis type reports, 13 reports official paralysis, 16 reports of lyme disease, and there are 19 reports of people reporting DR4 HLA type, 17 in people reporting other HLA types, and there were 76 people

reporting history of lyme disease.

I just wanted to emphasize that these events have a temporal, not necessarily a causal relationship with the vaccine.

This map illustrates the fact that the vast majority of the reports are coming from the mid-Atlantic and New England region, where lyme disease is prevalent, and probably represents use of the vaccine, although we don't have data on state by state vaccine administration.

This figure shows the frequency distribution of all VAERS LYMErix reports by calendar quarter. The number of reports is on the Y axis, the calendar quarter on the X axis. The white bars represent report numbers by date vaccinated, and the black bars represent report numbers by date reported.

You can see that most of the reporters were vaccinated in '99, in 1999, although about equal numbers were reported in 1999 and 2000. And this suggests some delay in reporting.

And it could be the result of stimulated reporting, from media coverage, of adverse events after LYMErix which began around the end of 1999. Delayed recognition of a connection between an adverse event and vaccination, or delayed onset of an adverse event.

This figure shows the frequency distribution of all VAERS LYMErix reports by age and onset. You can see most of the reports are in 40 to 50 year olds. There were 7 reports in people

less than 15, 34 reports in people over 70, which are outside of the recommended age range for the vaccine. This could reflect off label use, or errors in the reported age.

We don't know the age distribution of vaccine recipients, so we can't say if age is a risk factor for adverse events. We also know that about 53 percent of the reports were for males, 47 percent for females. And, again, we also don't know the gender distribution of vaccine recipients.

This figure shows the time to onset of adverse events after LYMErix. And as you can see most of the reports are on the day of vaccination, or in the next few days. This is a typical pattern of time to onset reported for most vaccines in VAERS.

You can also see that we have some reports many days after vaccination, and I think the longest is about 300 days.

This figure shows the previous distribution by dose, most of the reports are after the first dose. This table shows the ten most common coding terms reported to VAERS after LYMErix. And the italicized terms represent events that were associated with the vaccine in the trial.

So that you can see that most of the top ten events represent events that were reported in the trial. I would like to caution that the definitions used in VAERS for these events, the definitions in the trials, could be slightly different.

Also many of these events are non-specific, for

example, flu syndrome, and that is commonly reported after many vaccines.

There were four deaths after LYMErix reported to VAERS. They included two men who died from autopsy proven cardiovascular disease; a 43 year old man who developed arthritic and neurological symptoms, which he attributed, or which the report attributed to LYMErix, and that person committed suicide seven months after the second dose of the vaccine.

An autopsy was conducted and did not report any findings that could explain the symptoms, although it is not clear, from the report, what type of investigation was done.

The fourth death was in a 69 year old woman who developed anemia and thrombocytopenia seven months after the first dose, and died six months later, an unknown time after the third dose, the diagnosis of myelofibrosis, and no autopsy was conducted in that case.

And these deaths represent temporal, not necessarily causal, associations with the vaccine.

There were 85 serious reports, 44 reports of musculoskeletal events, which I will describe a little later. There were 24 reports of a variety of neurological events, including 5 reports of cerebral ischemia that included three cerebral vascular accidents, two transient Ischemic attacks.

The median age in the people who had those events was 62, and events of this nature are common in that age group.

There were also 5 reports of demyelinating events, two reports of optic neuritis, one 131 days after the vaccine, the other an unknown number of days after the vaccine.

Two reports of transverse myelitis, 10 and 13 days after the vaccine. And there was one non-specific demyelinating condition diagnosed 208 days after vaccination.

The remainder of the neurological events didn't fall into any single diagnostic category. There were also three hypersensitivity events, which I will discuss a little bit later, as well.

The remainder of the adverse events fell into a miscellaneous category with no clear pattern. This figure show the time to onset for the 24 hypersensitivity events, defined as either urticaria, or urticaria with respiratory symptoms after the vaccine.

And the two reports that are lacking represent a 39 year old woman who developed a red face, itching, and had the sensation her throat was closing within one hour of the second dose.

The second report was in a 39 year old woman who experienced itching, hives, chills, myalgia, labored breathing, nine hours after the first dose. Both of these patients were treated with epinephrin and steroids, and recovered.

And the close temporal relationship in the specific clinical symptoms and signs in these reports, and the other, or

some of the other urticaria reports, makes a causal relationship with the vaccine plausible.

The next exam reports coded arthritis, arthrosis, or rheumatoid arthritis, because of the link between lyme disease and arthritis, and the theoretical concerns that have been discussed.

Here we see the reports of thirty conditions by calendar quarter vaccinated in the white bars, and calendar quarter reported in the black bars. While most people who reported these conditions were vaccinated in 1999, more than reported in the year 2000, again suggesting delayed reporting, which could reflect either against stimulated reporting, delayed recognition of a connection between an arthritic condition, and the vaccine, or delayed onset of the adverse event.

As a remainder, in the pre-licensure trial there was on difference in the rate of arthritis in the vaccine and placebo recipients. In the VAERS reports of arthritis or arthrosis, and rheumatoid arthritis, we looked for patterns by age, gender, and dose.

There is no substantial difference in age among the arthritis reports, but we did note two patterns that are illustrated on this slide. For arthrosis reports, which are reports of joint swelling, you can see a male predominance. When a female predominance would be expected based on the female predominance for the diagnosis of arthritis in the general

population.

However, you will see that when we total all three of the coding terms, the gender is approximately equal between the two groups. We also found that for the coding terms arthritis and rheumatoid arthritis there was a predominance of these events occurring after the second dose, which persisted although slightly less for all the three coding terms.

And, again, this is not what would be expected based on the fact that most reports of adverse events after LYMErix were after the first dose.

So we further examined this dose trend by looking at time to onset by dose for the rheumatoid arthritis, and arthritis coding terms.

And we did this because if the vaccine is causing arthritis through a common immune mechanism we might expect clustering of time to onset.

This slide illustrates the time to onset for the rheumatoid arthritis reports, the first dose report is in white, and the second dose report is in grey. And as you can see there is a wide range in time to onset with no particular clustering.

Similarly for the reports coded arthritis we see the first dose in white, second dose in grey, and third dose in black, we see a wide distribution of time to onset, with some clustering in the first week, but this is what we would normally expect for reports to VAERS.

And we also see some reports with delay onset, and those reports also did not cluster and range from 11 to 39 weeks after vaccination.

We wanted to address this issue further, so we tried to characterize the clinical symptoms and signs in the reports that were coded arthritis, arthrosis or rheumatoid arthritis, and see if they mentioned any of the five factors, joint pain, limited motion, joint tenderness, joint warmth or joint swelling that is typically used for the diagnosis of an inflammatory arthritis, with joint swelling being the most suggestive.

So we see there that there are 58 reports that specifically mention joint swelling. And we further examined their time to onset by dose stratification and, again, see no unexpected patterns with a wide distribution of times to onset.

We also looked at reports of facial paralysis because of the association with lyme disease and facial paralysis. In the pre-licensure trial there was no difference in the rate of facial paralysis between the vaccine and placebo recipients.

In VAERS there were 13 reports. There was one unexpected pattern in that there were ten men and two women when we would expect approximately equal distribution based on the natural history of the disease.

Although, again, we don't know the distribution of vaccine recipients by gender.

We conducted a follow-up survey of the 12 people who had reported as of October 2000 to further assess these cases. We were able to contact 7, 5 were lost to follow-up.

Four of the seven had concomitant illness, including two with hypertension, one with hypertension and diabetes, and one with multiple cranial nerve palsies of undetermined ediology. That patient had headaches prior to vaccination which might have represented the onset of that disorder. Five of the seven have completely recovered.

We also looked at the time-to-onset of these reports and, again, we see a wide range of time-to-onset with a slight peak at four weeks.

Because of the theoretical concern of the association of the DR4 HLA type and treatment resistant lyme arthritis we further examined reports that included this information.

There were 19 reports that included the DR4 HLA type and 17 reports of other HLA types. The coding terms arthritis and arthrosis were more common on people who reported any HLA type, but the clinical characteristics and coding terms were similar in the two groups, and there was not a predominance of arthritic conditions in the DR4 group.

There were more reports after the second dose for both of these groups, but the time-to-onset was reported to occur over a wide range.

We also looked at the 76 people with the self-reported history of lyme disease, and here you can see their coding terms. We compared that with the ten most common coding terms for all reports, and what you can see is that there is some shifting in the order in which these coding terms occur, but the overall pattern is similar between the two groups, suggesting that people with a self-reported history of lyme disease report similar events, as others after LYMErix.

There are also 16 reports of people who reported they developed lyme disease after vaccination. The clinical characteristics in coding terms were consistent with lyme disease in this group.

Fourteen of these people developed lyme disease after their first or second dose, before completion of the vaccine series, and may not have achieved adequate immune response, possibly resulting in acquiring natural lyme disease.

A few of the reporters were concerned that the lyme vaccine had reactivated a previous lyme disease, or somehow influenced the course of lyme disease. But it is not possible, from the reports that we have, to evaluate this.

So, in summary of the VAERS analysis, VAERS has limited ability to asses the causal relationship of adverse events in vaccines. However, hypersensitivity reactions reported to VAERS are common, but can be plausibly linked to LYMErix because of their specific timing, shortly after vaccination, and their

clinical features, specifically urticaria and allergic respiratory symptoms.

The question of the association of arthritis with LYMErix cannot be resolved with VAERS data alone, although the reports of arthritic events reported to date do not provide clear evidence of a causal association.

We are attempting to gather additional information on people who report joint problems following LYMErix by conducting a telephone survey. We are looking at events that have been coded as arthritis, arthrosis, rheumatoid arthritis, joint disease, or arthralgia, in order to obtain detailed information about the events including medical records.

We intend to look for patterns of unusual disease or laboratory values in these reports. We also want to confirm the diagnosis of arthritis for a case control study, which I will discuss in a moment.

And as of last week we have completed 35 of approximately 200 planned interviews.

We want to further study this question by conducting a case control study based in VAERS. We will use arthritis cases confirmed by the survey, and compare them with two control groups, also identified through VAERS, that would include arthritis cases reported following other vaccines, and events other than arthritis reported following LYMErix.

Our intent at this time is to conduct high

resolution HLA typing in all three groups, and test for t-cell reactivity to OspA and LFA1.

Probably only a very strong risk will be detectable in this study, because of the relatively small numbers of arthritis reports in VAERS. But if the results are suggestive of an association additional studies will be conducted as needed.

At present the protocol for this study is still in development.

So, finally, our plans for continued safety evaluation of LYMErix include continual monitoring of VAERS reports, conducting a VAERS based telephone survey, a planned case control study to further evaluate joint problems following LYMErix.

And, of course, the results of the maintenance sponsored phase IV study will be very important to help evaluate safety concerns.

I would just like to acknowledge the others at the FDA and CDC who helped to analyze this data. Thank you.

CHAIR DAUM: Thank you very much, Dr. Ball. We have a few moments for questions regarding Dr. Ball's presentation on the VAERS data. Ms. Fisher.

MS. FISHER: Dr. Ball, you stated that it does not provide clear evidence for an association with arthritis, but it must be enough of a concern for you that you are doing further studies, I see.

Is there any plans, in the one control group, arthritis cases reported after other vaccines, are you going to be looking at the genetic profile of those individuals to see if, since 30 percent, I think the DR4 allele, is there going to be an attempt to look at whether or not there is some sort of an association?

DR. BALL: The idea behind the case control study is to look at HL type in both the cases who develop arthritis after lyme vaccine, as well as the two control groups. So we will try to address that.

CHAIR DAUM: Questions, comments?

(No response.)

CHAIR DAUM: Okay. Well, the -- you must be hungry. Thank you, Nancy, for reminding us of basic biology here.

It is now 12:28, coming up on 12:30. We will take a break for lunch and reconvene in one hour, at 1:30

(Whereupon, at 12:30 p.m. the above-entitled matter was recessed for lunch.)

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

(1:35 p.m.)

CHAIR DAUM: Good afternoon, we are back in session. Committee members needing a jolt of caffeine will be pleased to know that a new pot of coffee will be forthcoming in a few moments, we hope.

We turn now to the -- everybody sort of settle down, please. We turn now to the open public hearing portion of today's session. As of last count we have 17 people who have indicated a wish to speak.

We are going to have to move on a strict schedule because we need to have time for the committee to digest, deliberate, and then discuss all of the data that they've heard today.

So I'm going to be a little more ruthless than usual about asking people to adhere to the time limits that we've all agreed to, and mentioned before.

What I'm going to do is to call three speakers names in a row, and asking one to begin, and the other two to sort of get ready. The options are to use the microphone that is just behind the committee tables, near the cameras, or to use the podium. Either is fine, but the same time limit applies, and I would appreciate your cooperation in that regard.

So the first speaker is going to be Karen Vanderhouf Forschner, who I know is up here already. The second

is Stephen A. Sheller, I hope I'm not butchering anybody's names, I apologize if I am. And the third one is Jenny Marra.

So let's begin with Ms. Forschner, please.

MS. FORSCHNER: Good afternoon, and thank you for having me here. I'm with the Lyme Disease Foundation, which is the only national lyme disease group meeting federal standards as national.

I have a disclosure to make. We have always supported vaccines, throughout the Foundation's history, funding vaccines, and encouraging their development. We have testified at FDA and CDC meetings for this.

We also received, this year, a grant of 120,000 from SmithKline Beecham, which is part of a matching grant challenge from 1999, and there will be additional donations for the year 2000.

We have, I'm the mother of a child who had lyme disease, who died of lyme disease, and I have not taken the vaccine, though I was willing to enter the trials.

And my daughter, who was born subsequently, is healthy, and we were going to have her on the trials, too, though she was sick.

We have concern over the scientific evidence and criteria being not completely scrutinized and published. We are concerned about the closed loop and difficulty of other opinions and scientists getting into these government discussions and

looking at the data.

We are concerned about conflict of interest. We know that there were HLA studies done, from what we understand, in phase II, we haven't seen it. There is significant amount of research that has been done, much to SmithKline Beecham's credit, that hasn't been published, unfortunately.

We are concerned about informed consents to patients, both with prior lyme, and on the HAL issues. There has been data compiled for adverse outcomes. We are concerned that the data that was captured before is still the same data that you are capturing now, and may not actually represent what is actually happening to the patients out in the real world.

We are concerned about the definitions used for vaccine failures. We are concerned about definitive lyme, and probable lyme, probable lyme I haven't seen anything up here on the screen.

We are concerned about the misuse of the vaccine in people that are older, and people under current treatment for lyme disease. We have concern about patients not being able to get into the VAERS system, which we have been hearing for years, for adverse events.

Doctors and investigators not reporting their patients as having problems, and fear of patients getting the vaccine from family practitioners, that they don't want to go ahead and say that they've had problems, it might affect their

relationship long term.

As you know the science in the vaccine, and I'm giving the committee a tape, is 36 percent of the patients in the trials remain zero negative. Those were the ones that were culture and PCR positive, which means there are some people that will be zero negative, and may fall through the cracks.

We are concerned that only 60 to 70 percent of those people had EM rashes. I have four exhibits to show you. I think you can still hear me as I move over here.

As you know, in '93, there was -- and this material is just the front page of the material provided to the members here. In '93 there was an active discussion going on on HLA typing, that apparently may not have made the informed consent forms.

In '95 one of the investigators wrote to the National Institutes of Health and said that he was working on the trial for SmithKline Beecham, and a percentage of the patients developed joint pain or arthritis following vaccination.

He was going to be studying the HLA profiles, and he continues to be concerned about the phenomenon. My concern is, did this person ever tell SmithKline Beecham? Did they tell the internal review board, did they tell the data safety and monitoring board, did they tell the FDA since it went to the National Institutes of Health, and certainly did they tell the patients at the time.

There is a scientific article that I think was excellently done. Eve O'Day is co-author of it. What they have done is looked at monkey models, and what they showed here, that vaccinated monkey models were zero negative, there was no culture in the ticks, borrelia burgdorferi, there was no culture from the animals, but they found a low level of transient infection in the patients.

There is another interesting article that was published in '97 that showed that the vaccine may cause a state of partial immunity. I'm not saying that this is actually happening. I'm saying that this was in the scientific literature, and it was in the debate at the time. Did this translate to informed consent to the public?

What is happening out in the real world, even today, is patients are not getting into the system, they are having trouble reporting to their doctors, and they are having trouble. So there is an example of a letter that went in that my doctor would not report me as an adverse event in the trials.

And finally one that was, second to last, one that was more recent, and more home for me, since it is in my own home town, this patient had a doctor who gave him the LYMErix vaccine in the second week of treatment for lyme disease.

Three doctors in the practice had said it was perfectly safe to take it while you have active lyme disease, and actually gave it to the patient. In other conversations with the

doctors, separate from this, they had indicated that they felt under pressure since they had invested so much in the LYMErix vaccine to actually use it, and get it off the shelf.

Finally, there is an issue of cost effectiveness of the vaccine. The letter to the editor said, maybe instead of treating everybody in a large region to prevent it with a vaccine, with risks that still indeed continue to be questioned, maybe it would be better to treat just that small population that had a tick bite, and treat the tick bite with 15 dollars worth of antibiotics.

Right now I weigh the question about the vaccine myself, since I lost my son, and I would like a vaccine. I'm done. What I'm concerned is that right now I protect her with tweezers, and if she actually were ever to need it, I would ask for antibiotics. But right now I do tick checks, and I use tweezers.

And I'm afraid that this is a vaccine that may be a very good vaccine, worthy of all of our support, that has a bad reputation, or a vaccine that may have actually slid through the system on science that didn't quite build it up, and may not be worthy of being there.

And I think it is owed its due to get the answers verified.

CHAIR DAUM: Thank you very much, Ms. Forschner. And we will next call on Mr. Sheller, then Ms. Jenny Marra, and

Dr. Sidney Wolfe. Mr. Sheller represents, or is associated with the law offices of Sheller, Ludwig, and Bodey.

MR. SHELLER: Thank you. You know, sometimes I feel you are like a jury here, that is going to only hear one side of the situation. My recommendation to you is that for your next meeting you invite some speakers who can portray to you additional information.

For example, Dr. Rose from the Dupont Children's Hospital. You might even consider inviting the chief surgeon from the hospital, who was knocked out of surgery because he participated in a trial and got arthritis from it.

So what I'm suggesting to you is let's consider this committee having the full kind of flavor, instead of just five minute talks by a bunch of people, from at least some scientists that they can portray, give very good questions, you've asked tremendous questions, and I appreciate the effort you are making.

But let's have a trial where you get to hear the whole case. In any case I'm here to urge this committee to recommend the moratorium, if not withdrawal of LYMErix, or at the very least recommend substantially enhanced warnings for the vaccine.

With spring quickly approaching the time for action is now. People who started the vaccine schedule last year are coming due for their third shots, and additional people may start

the vaccine schedule with their first and second shots very soon.

Therefore the committee has a chance now to save some people. And you can do your job by doing it right away. And I will give you some examples, but you are going to hear a bunch of people testify, and I prepared a document which you have, which outlines a bunch of papers, and materials, and I hope that you read it.

We put a lot of time and effort into it, and we try to bring you some expert testimony, but unfortunately we were not able to get the people to come, who had information, because they said for five minutes I can't just come here and do this.

Now, keep in mind this. And this is something I'm adding. I heard Dr. Ball talk about the study he is doing. I appreciate he is doing a study, I'm disturbed that the FDA waited all this time to get around to doing it.

But most importantly the numbers, and I think there is a chinese fortune cookie that says, when all else fails, manipulate the numbers. But apart from that, I don't mean to joke, this is very serious.

But what I want you to do is keep in mind that there are 1,076 adverse events as of October 31st. There were, supposedly, 1,450,000 doses distributed.

I don't know what the word distributed to me is, but I know from doctors who have the vaccine, it is sitting on their shelves in a lot of cases. So my guess is that there are a

lot of doses distributed that haven't been injected into any patient.

Equally important, the adverse event reporting system only captures a very small percentage of adverse events. And this has all been said, and there has been delayed reporting of a number of adverse events.

So you have 1,076 events -- and remember, most people get three shots, some as many as five. My guess is those -- you may have 100 to 150,000 people, at most, vaccinated. We have found that the real problem seems to occur after the second shot.

We have also found that a reaction on the first shot, and I've gotten calls from over 200 people, we don't advertise, we don't solicit, these are clients that I represent, some of them extremely seriously ill.

And I'm just saying to you, if they have 1,076 adverse events as of October 31st, do some quick numbers in your mind, multiply it by 10, at least 10. That is 10,000.

Assume that may be 100,000, 150,000, build it up if you want, but just do some quick numbers, add some lag time to that, you've got an awful lot of adverse events being reported here, an awful lot.

And you ought to take a real close look, because the system for collecting adverse events doesn't really tell you much. In fact that is what I heard about the studies being done

by SmithKline. They draw conclusions without revealing how many shots were administered, which is key, I'm telling you, it is after the second and third shot that people really get -- and you will hear that today.

What else you will hear is that there are studies that are being done. And not only by SmithKline, and you need to invite these people to speak to you.

I'm trying to get all this in, in five minutes. One of the worse things we've seen is physicians are failing to recognize adverse reactions to those first and second shots, very serious problem.

We have some poor client in the -- and what they do is they then get the third shot, even though they are suffering some adverse event, and then they are wiped out.

But, for example, we have seen people being -- we have one client from Peoria, Illinois, who was told that he needed his coccyx bone removed, and he had a reaction to the vaccine. The doctor had no inkling that is what was going on. He was operated on, developed osteomyelitis, and he is finished.

We have other clients who have gotten carpal tunnel syndrome diagnosis, and had operations on their hands. The doctors aren't being given information in the labels, they are not being able to properly be warned.

You can't get a -- you know how labels work. Most doctors say they read it, but they look at the warning section,

and then they stop. And if these things aren't in black boxes, this HLA situation for example, I think is key.

And I see what SmithKline said, basically today, and I see you -- the HLA situation has not been adequately studied. Dr. Steere is studying some of it, but I refer to a case in our papers, where Dr. Steere does some peptide blood work, but he says in his studies, you are supposed to do synodal fluid to find out about that.

And I mentioned that. Now, why? And you will hear one of these patients talk about their synovial fluid, even though swelling was never tested. And they were diagnosed as having an event, by their treating physician, relating to the vaccine that is extremely serious for them.

Thank you.

CHAIR DAUM: Mr. Sheller, thank you. We next call on Ms. Jenny Marra, followed by Dr. Sidney Wolfe, and Ms. Kathleen Dickson. Ms. Marra?

MS. MARRA: My name is Jenny Marra, I'm a hospice nurse from New Jersey. I'm also a LYMErix vaccine victim. I have been living with severe joint and muscle pain since getting the vaccine in early 1999. I'm also HLA DR4 positive.

I would like to start by quoting the chairperson at the FDA committee that approved LYMErix, Patricia Ferrieri. "I might comment that this is fairly rare for a vaccine to be voted on with such ambivalence and a stack of provisos."

The entire panel had concerns about the long term outcome of this vaccine due to the fact that it had only been studied for 20 months. They were also concerned about the theoretical possibility that this vaccine, made from the OspA protein, could cause an untreatable, incurable form of arthritis in 30 percent of the populations.

In fact, the head of the clinical studies, Allen Steere had said: "This is an issue of concern, on-going surveillance will be important."

Steere had published an article in Science Magazine on this topic five months prior to the approval of LYMErix. The article is in the vaccine victims packet I've given you.

SmithKline was so concerned with this issue that they had study participants sign a paper indicating the theoretical possibility existed that vaccine, that the vaccine might cause arthritis in certain genetically susceptible individuals.

Yet SmithKline did not include this information in the product labeling, or inform the health care providers of this concern. Had I known this I personally would not have taken the vaccine.

I have obtained the VAERS reports up to May 8, 2000. They are a little different than what I heard today. During this time there were 467 reports. Out of those there were 146 reports of joint pain and/or swelling.

I have studied these for over a month, and going by the wording of the complaints, noted pain in the joints, joint pain, swelling, arthritis, and that is all that I included, I didn't even include most that he did.

And as most of us are aware, 90 percent of the adverse reactions are not reported. So there are many more people that are suffering from this vaccine that we don't even know about.

SmithKline knowing this theoretical possibility, even went ahead and tested it on children before knowing the long term outcomes on the adults. To me this is outrageous. This just shows the heartless disregard that SmithKline has for the children and adults of this country.

This is pure profit motivation. It is the only way to explain the total lack of concern for the public. I have done TV and newspaper interviews to educate the public of the devastating effects of this vaccine.

From this I am contacted daily by people harmed by this LYMErix, some of which are here today. Others cannot make it because of the illness they have gotten from this vaccine.

I have been told by some that they have tried to contact SmithKline about the reactions. They are put on hold until they give up and they just hang up the phone.

A few of the people were in the clinical studies. I have been told by them that they would go to SmithKline with

different problems that were happening to them, and SmithKline would not document the reactions they were having.

One study participant, Lewis Ball, wrote a letter to respond in an article in the New London newspaper that states: "I am part of the original test group that got the vaccine mentioned in this article. On two different occasions I contacted Dr. Sisken with health problems that I wanted to be part of the record on the study, into the heading of possible side effects."

"I was told, on both occasions, that there was no column to file these health problems in, because they weren't expected. One involved sudden memory loss, and the other was much more involved."

In the VAERS report I have there is a 43 year old gentleman that you heard of earlier, that committed suicide seven months after getting this vaccine because the pain is so severe, and from being unable to get relief from 14 doctors he had seen.

I can relate to this man's pain, as can most of the 75 people I have spoken to, that have been hurt by this vaccine. Most of us agree that if it was not for the support of our families we would not -- we would have done the same as this vaccine victim.

This is how severe this pain is we are living with every day. We have all seen several doctors looking for help. Our health care providers are turning us away with statements like "I don't want to get involved".

That is what a rheumatologist told me and my husband a few months ago. This is the attitude a lot of the health care providers, these people hurt by the vaccine are dealing with.

This vaccine is not causing just some minor joint pain, it is destroying lives. It is destroying the lives of our most healthiest population. These people being vaccinated are healthy outdoor people.

They thought they were protecting themselves from a horrible disease. Instead they've gotten an even worse disease, one that cannot be treated or cured.

We all would have been better off getting lyme disease. SmithKline wants this vaccine approved for children. I know a few children that were in the studies that have already been severely hurt.

From what I can gather, from the study participants I have spoken to, SmithKline's adult studies were tainted. How can we trust the children's study results?

I ask this panel today to recommend that this vaccine be stopped immediately. If you cannot pull it, at least put it on hold until the studies that you are talking about today are done.

It may be too late for us vaccinated, but it is not too late to stop the destruction of more lives. Thank you.

CHAIR DAUM: Ms. Marra, thank you. The next

speaker is Dr. Sidney Wolfe, followed by Ms. Kathleen Dixon, and Ms. Kay Lyon.

DR. WOLFE: Thank you. This is the first time in more than 20 years --

CHAIR DAUM: Can you speak right into the microphone, Dr. Wolfe. Do you want us to help you adjust it?

DR. WOLFE: This is only the second time in the almost 30 years since I left NIH to start this group, that we have become involved in some vaccination or vaccine issue.

The first was the swine flu. And although there are a number of differences, such as the high mortality disease influenza was more meritorious generally, not the swine flu, but of having immunization.

But there are also a lot of frightful similarities. One is that in the case of swine flu, the vaccine caused an autoimmune disease called Guiembre.

Secondly, there was a gross overselling of the vaccine for what amounted to a few cases in Fort Dix, New Jersey, there was a recommendation for nation-wide immunization.

So those similarities are where I would like to start, and just simply say that when, and you all know this, when you evaluate a vaccine you have to look at the benefits, which are a function of what the risk of the infection is for someone, which in this case varies enormously around the country, and the effectiveness of the vaccine.

You have to look, obviously, at short term and long term effects of the vaccine. And, finally, in combination you have to look at the benefit risk ratio.

But equally important, and this was the tragic lesson of the swine flu vaccine, one has to look, when one sees a very questionable immunization campaign such as this going on, about the implication and the negative effect on public health, generally, and on vaccinations in specific.

I mean, a huge setback was dealt by the really ill-conceived swine flu vaccine, and I'm afraid that already, and it may even be worse later on, with what is going on with this campaign, it will deal another setback.

As several people have mentioned, you voiced some concerns when this was discussed for approval in May of 1998. There is some new information since then.

If you go to a website called LYMErix.com, you see some extraordinarily reckless promotion of this vaccine. The first page shows backyard fun, golfing, gardening, pet owner outdoor sportsman, don't let lyme disease interfere with these activities.

You then can go on to another page and see that lyme disease, if you check the backyard for grilling, may be as close as your backyard. And there is a little cartoon movie there that shows someone in the backyard grilling, getting bitten with a tick.

You later get on to see a map of the United States. We have complained about this ad, which is what it is, and hopefully -- the FDA has actually agreed to look into it.

Another problem related to the gross overuse, even if there were any appropriate use for this, is the failure right now for the labeling, and certainly the promotion to fall in line with the ACIP recommendations of 1999.

The ACIP recommendations stressed, very clearly, that it is a combination of where you live, and the kinds of activities you are engaged in. So that, for example, persons who live in a high or moderate risk area, it is not recommended that they get vaccinated if their exposure to tick infested habitat is minimal or none.

Anyone, regardless of what kind of activity they are engaging in, is not recommended as having a lyme vaccination if they live in the low to no, or very little tick kinds of areas.

Related to this is the labeling. And I think that one thing, aside from whether or not you believe a moratorium should be put forth, which I think a reasonable argument could be made for, the current labeling, outside from the advertising, is really off the wall.

Nowhere in the indications section is there any mention of geography. That is mentioned in a separate section on epidemiology. It simply says individuals most at risk may be those who live or work in borrelia burgdorferi infected, tick

infected grassy or woody areas, landscaping, brush clearing, forestry, and so forth.

And it doesn't really get into the geography. Obviously you have to combine both. This label really needs to be changed.

Other new information is this very interesting study published in 2000, an animal model in hamsters showing that vaccinating them with this antigen, the OspA antigen, and then subsequently exposing them to the bacteria, the spirochete, developed destructive arthritis.

And in the conclusion of their paper they said OspA vaccine should be modified to eliminate epitopes of OspA, outer surface protein antigen responsible for the induction of arthritis. These are people from the state hygiene lab in Wisconsin.

There also have been thoughtful studies by the CDC, by Dr. Melsorn, an economist there, and by the IOM, raising serious questions about the benefit risk ratio on this. The IOM placed this whole idea in what they call their less favorable category, the lowest ranking in priorities of vaccine development, just because of the fact that A, the vaccine is not extraordinarily effective; B, it is not preventing a life threatening disease; and C for most people a successful antibacterial intervention can occur not when you have a tick, but when you have some clinical symptoms that are suggestive of

actually beginning to have lyme disease.

What recommendations would I make? Well, I think that the idea of surfing for a safer vaccine, if one is going to go ahead with vaccination to prevent this disease, certainly is a good one.

We have seen enough other instances, in the history of vaccines, where one comes up with an idea of a safer vaccine, and a safer vaccine is always better, particularly when the benefits of this are so questionable.

And, secondly, as I mentioned before, immediately require changes in the labeling, not just with respect to the indications, which are flawed, and missing entirely anything about geography, but also the warnings.

I think that the labeling should include a lot of information that is missing now, such as this very, very worrisome animal study model for developing arthritis.

Secondly more information about the fact that HLA D4 has clearly been linked, in the case of post-lyme disease arthritis, as a risk factor, and it is reasonably likely that the same will occur here.

And, also, I think that in the labeling needs to be some explanation about some of the very well documented post-vaccine cases that you will hear about today, and which I think are clearly there. These are documented cases of arthritis in people shortly after they took it.

I think the company should be forced to send a letter out to all physicians reflecting the change in labeling that I hope you will recommend.

In conclusion, one sentence and I'm done, I think it is highly likely that the majority of people in this country who have been vaccinated with the LYMErix vaccine have had an unfavorable benefit risk ratio when they were vaccinated.

As a matter of public health policy it is important to do everything to minimize the damage that may be done from the use of this highly questionable vaccine.

CHAIR DAUM: Thank you very much, Dr. Wolfe. We would like to request, again, one of our operating rules here is that there is no flash photography, please. I hope you will all respect that.

In an arrangement with Ms. Cherry, Ms. Dixon has been accorded seven minutes, two extra minutes.

MS. DIXON: My name is Kathleen Dixon and I am an analytical chemist from southeastern Connecticut. I would like to talk about the validity of the LYMErix adult trial, specifically the validity of the serological standard used, and how that standard affected the vaccine trial results.

The problem is the deer borne IgG standard. One of the testing procedures used in the trial, the western blot, looks for antibodies to specific antigens expressed by borrelia burgdorferi.

The limitation of the western blot is that it qualifies the body's reactions to the infection, but does not actually quantify, or identify the infectious agent.

In lyme disease patients produce variable antibodies over time. I want to point out the IgG response in these patients appear in a characteristic sequential pattern over months to years, to as many as 11 spirochetal antigens, the appearance of new IgN response, and the expansion of IgG response, late in the illness, and the lack of such responses in patients with early lyme disease alone, suggests that borrelia burgdorferi is alive throughout the illness.

And, again, Steere reports that in the body of the Dressler report, which I included in the data package for the FDA, the specific immune response in lyme develops gradually over a period of months to years, to greater than or equal to ten spirochetal polipeptides.

I want to point out here, of the 237 patients presenting, this is from the Dressler-Steere report, 54 met Steere's criteria for lyme disease, and these showed IgG criteria 0 causivity to 72 percent.

The majority of these were lyme arthritis patients, and arthritis patients always have a higher antibody response, it is supported in all the literature.

Back in 1994, '93, the CDC decided that they wanted to establish a new zero diagnostic standard. We assume it is to

facilitate these vaccine trials. In May of '94, this was prior to the Dearborne Conference. The Dearborne conference was in October of 1994, members of the CDC met and decided that the Dressler-Steere standard criteria for IgG of five of ten bands, should be the zero diagnostic case definition to be used in the vaccine trial.

And this shows the data sets that they chose, that the studied in the Dressler report, and it shows the bands representative from the arthritis data set only, and just ignored neuro brulliosis.

So the problem with the IgG standard is that they calculated that there should be five of ten bands, and that would be a 99 percent specific for borrelia burgdorferi. That was not empirically derived, that was not based on any patient data set. They never showed that, characteristically, 80 or 90 percent of all patients with lyme disease have five of ten bands.

This data, from this Dressler report, was generated by borrelia burgdorferi strain G-39-40, a strain which Barbara Johnson of the CDC later, at the Dearborne meeting, recommended not using.

And it artificially represents a summary of what the arthritis only presenting patients showed over time.

Dressler and Steere report, in the Dressler report, that individual specific bands, such as OSP A, B, C, 1893, and 28, generated from a B strain G-39-40, are specific markers of

infection.

Confoundingly, OspA and OSPB were left out of the Dressler IgG Dearborn case criteria. And, therefore, the Dearborne case criteria using the LYMErix trial, excluded to Steere, major immunogenic outer surface proteins from the case criteria, OspA and OSPB.

So we really don't know what Dearborn case definition means. It doesn't mean -- we really don't know.

But what this has affected is that Dearborn case definition misses a lot of patients. Instead of weighing the specificity of an individual band, such as OSPC or P93, both highly specific alone, it will result in the patients lost opportunity for early and successful treatment.

This was the previous sera diagnostic standard, according to the CDC. The third one says, significant change in IgM or IgG antibody response to borrelia burgdorferi impaired and acute phase convalescent serum samples.

Although potential useful in confirming active lyme, neither cultural isolation or paired serum specimen testing has been used much for validating cases of routine lyme disease surveillance, since the procedures are not often performed in a general medical setting.

That used to be the case definition, changing bands over time. You saw that Allan Steere said that earlier, this is a borrelia, borrelia have antigenic variation, you show different

antibody profile over time.

So we believe what -- how does this apply to the vaccine trial? If few people have lyme disease, and this is Dressler Dearborne criteria will exclude most patients with lyme disease, the vaccine will not be shown to be a failure, or cause adverse events. And we believe that is exactly what happened in this trial.

This is the New England Journal of Medicine report of the 1998 LYMErix trial. Only 22 people got lyme disease in the vaccine group in the first year, while there were 515 unconfirmed lyme cases, compared to the placebo group, of 468.

The following year is no significant difference, but there were ten percent unconfirmed lyme cases in the vaccine group than there were in the placebo group.

As Dr. Luft alluded to earlier this morning, the western blot serology from these unconfirmed lyme cases will need to be reviewed for evidence of other BB specific bands, and compared to the placebo group by an independent group of analysts.

If there are any other specific bands besides OspA the case must be counted as lyme disease in the presence of symptoms. Note that there were only two asymptomatic cases in the first year of the vaccine group, versus 13 of the placebo group, and in the following year there were zero asymptomatic cases, and 15 asymptomatic cases in the placebo group.

We believe that these results do not show that the

vaccine is effective at preventing asymptomatic lyme disease, but rather that it is turning asymptomatic lyme disease into symptomatic cases.

Continued follow-up on these unconfirmed patients should have been with further western blotting from one of the CDC recommended strains, and the original case definition, which would be to look for changing bands, or any other specific bands besides OspA.

Or maybe one of these newer antigens D complexing messenger has been developed at SUNY and by Leonard Siegel.

We already discussed this earlier. It was mentioned earlier that an adverse vaccine event can't be distinguished from vaccine failure. An adverse vaccine event in a previously infected asymptomatic lyme patient.

An asymptomatic BB infected adverse LYMErix event case may never be detected until the patient is vaccinated and symptoms occur, which we think explains the majority of adverse events regarding LYMErix.

Many previously infected lyme cases report systemic symptoms after vaccination, and many find out they had lyme disease after being vaccinated, becoming ill, being tested for lyme disease, and finding other specific antibodies.

The FDA should, therefore, not be looking just for arthritis as a potential adverse event, but rather -- and not to the exclusion of systemic illness.

According to Allan Steere the rate of asymptomatic infection to symptomatic infection is one to one. So that for every person walking around with lyme disease that has symptoms, there is a person walking around with asymptomatic lyme disease. And we think those people are at the greatest risk.

Vaccine failure and exacerbation of asymptomatic infection are identical according to the patient data collected and on the on line VAERS data base.

The Dressler Dearborne Steere standard is not a valid criteria for assessing lyme disease, the former CDC criteria of changing bands is more valid. Until there is an independent review of the western blot data from the SmithKline Beecham adult trial, we have no idea how safe this vaccine is, it all needs to be retabulated.

Am I done? Okay.

CHAIR DAUM: Thank you very kindly, Ms. Dixon. We have next Kay Lyon, followed by Emily Biegel, and Lynn Lane.

MS. LYON: Good afternoon. I'm Kay Lyon from Windham Massachussets, a highly lime endemic area. I'm a member of a group advocating for lyme patient rights, and lead a line information and support group in my community.

In the past few months members of our group have read through much of what has been written on LYMErix, especially the material provided by the CDC and FDA.

Today I would like to present what we see as two

realities. The reality facing my community in Essex County, Massachussets, where children play in the woods, and on sand dunes where deer and field mice abound, and the reality constructed by SmithKline Beecham.

It appears from our research that the children of Massachusetts and elsewhere have paid a high price to clear the way for the approval and marketing of this questionable product.

How can this be, you might ask, when our children haven't been vaccinated? As our group reviewed the material from the government these facts were clear.

In spring of 1994 to enable clinical trials for LYMErix, SmithKline Beecham, the CDC, and the FDA held a special meeting to agree on a case definition for lyme disease. We just heard Kathleen talk about the changes that they made, which included a stringent serological definition.

In October of 1994 at another meeting in Dearborne, Michigan, these stringent serological criteria were extended to cover all lyme disease studies and serve as the official buyer for doctors to determine what they report as lyme to the CDC.

The CDC agreed to these criteria to help analyze data and report. But the criteria were not to be used by doctors to make the diagnosis of lyme disease.

The CDC maintained that lyme disease was to be diagnosed based on clinical review of symptoms, patient activity, and possible exposure to borrelia burgdorferi.

Despite this recommendation by the CDC when making a diagnosis most pediatricians and primary care doctors refer to the CDC criteria for reporting in an extremely rigid way.

As a result our children get lyme disease and are not diagnosed and treated in a timely fashion. Many of our kids get very ill before doctors are willing to treat them with antibiotics.

And even then the majority of doctors are not willing to treat a child if he or she does not meet the serological requirements for CDC reporting of lyme disease.

The CDC's 1999 initial report recommending the use of LYMErix stated OspA was not expressed in natural lyme disease infection in humans, a statement clearly refuted in the 1998 FDA Hearing on which those recommendations were based.

Further research shows the CDC retracted that assertion some three months later, stating that OspA, the antigen used for this vaccine, is in fact expressed with increasing vigor as natural infection disseminates.

In light of this correction we must ask that the agency also revisit the recommendation for the use of the LYMErix vaccine. This vaccine is made of recombinant outer surface protein A.

Despite the fact that the antibody reactions to OspA and OSPB are highly specific for lyme disease these bands were removed from the CDC criteria for reporting lyme disease.

This is a disaster for the children of Essex County, Massachussets. Outer surface protein A is expressed with increasing frequency as untreated infection disseminates.

And in Massachussets we see that many of our sickest children end up showing this band on the western blot. However, because of the CDC strict serological criteria the laboratories and the doctors they report to do not consider this band diagnostically significant.

We are concerned about the phenomenon of sera positive asymptomatic infection, which Allan Steere has stated occurs as frequently as symptomatic lyme disease.

In the last FDA Hearing on LYMErix Pat Coyle called this form of infection smoldering. Many have expressed concern that the vaccine might be a trigger that turns this smoldering infection on, converting it almost instantly into late stage disseminated lyme disease.

We also note that in the vaccine trial those whose sera converted were treated with the antibiotic, whether they had symptoms or not. This was, of course, the humane way to treat study participants.

But it is absolutely not reflective of medical practice in the real world our children live in.

In summary I am presenting to you two very different worlds. In the world in which my family and friends live we have children who live at risk in an environment teeming

with the lyme disease spirochete borrelia burgdorferi.

We have doctors who almost universally will not treat lyme disease unless it has been confirmed by the faulty criteria set by the CDC for reporting lyme disease, created initially to enable this vaccine.

We have children who get bitten and are never treated because our doctors do not understand the CDC recommendation that lyme is a clinical diagnosis, not a serological one.

We have children who get bitten and infected but are asymptomatic, unlike their counterparts in the vaccine trials, they are not treated and as Pat Coyle said, they are left smoldering.

Because of all of the above it is impossible for us to know which of our children are infected, and which are not. It is therefore impossible to gauge the true safety or efficiency of this vaccine, efficacy of this vaccine in this population.

It is also impossible to know which of our children, when challenged by OspA might have a dormant or subclinical infection rev suddenly to late stage illness.

On the other hand in the world of SmithKline Beecham data we do find LYMErix, we have an experiment whose success is based, in part, on a set of criteria created to enable the success of the experiment.

This is the proverbial circular reasoning

scientists are supposed to avoid. There is a significant gap between the world my family, friends, and I inhabit, and the world shown in data defining the study of LYMErix.

In light of this for parents everywhere I stand before you to say the gap must be bridged before we consider, even remotely, the notion of vaccinating any of our children.

Also, most importantly, the CDC's strict serological guidelines must be changed. Thank you.

CHAIR DAUM: Thank you, Ms. Lyon, very much. The next speaker is Ms. Emily Biegel, followed by Ms. Lynn Lane, and Mr. John Hardy. Ms. Biegel, please, thank you.

MS. BIEGEL: I'm Emily Biegel but I'm here to talk about my husband John. Some of you may have seen him come in with a walker.

John is an active outdoorsman and so I had the bright idea, a year or so ago, that he should -- that we should both receive the lyme vaccine. He had lyme vaccine on April 13th and May 11th.

He was frequently exposed to tick bites in his leisure activities, and we thought this was good idea to protect him, although as an aside I should say that we have labradors and golden retrievers, and do not give our dogs lyme vaccine because Cornell doesn't recommend it.

So we made a decision for ourselves that we spare our dogs from. In July he started neurological symptoms which

were initially diagnosed and Guiambari syndrome, and subsequently in September, when he was not responding, but continuing to deteriorate as chronic inflammatory demyelinating polyneuropathy.

And this, really, has -- it was just like floodgates opening to a nightmare that has turned our lives, and the lives of our friends, family, and work colleagues, upside down.

Six months later he has had four hospitalizations, a lot of atrophy, insulin dependence, depression, yeast infections, compression fractures, edema, tremors, and 25 plasma for reeses treatments.

It is a bitter harvest that we've reaped. His neurologist has -- the neurologist, not we, has reported this to VAERS as a vaccine adverse event. John is now profoundly disabled. He spent 33 years training guide dogs for the blind, walking ten miles a day, doing all kinds of physical activities like gardening in his spare time.

Now he does physical therapy, and he sits in a chair with his feet elevated. He bought a kayak a few weeks before he got sick, and every time I look out in that backyard, at that kayak he has never had a chance to use, it is an ugly reminder of how our lives have been changed by a decision to do something that we thought would be helpful.

If you tell me that LYMErix is statistically safe to take I will tell you to imagine, for a moment, that you are

John, and your life, your work life, your social life, your driving, everything that is part of your day to day functioning is taken away from you.

And then you will know that this is a terrible place to be, and the worst of it is that it could have been avoided. Thank you.

CHAIR DAUM: Thank you, Ms. Beigel. While I appreciate the sincerity and the effort that it has taken every individual on the program to come and communicate their views to the committee, I would ask that everybody hold their applause, because I think it is important the committee hear and digest, and that we have as much time as available, as possible available for this.

So if you would, please, listen and let's emote together, but let's hold the applause in between speakers.

Ms. Lynn Lane is next, followed by John Hardy, and Pat Smith. Ms. Lane, please.

MS. LANE: Hello. I have handed out several copies of the original story about my lyme disease vaccine trial study experience. There are more available if anybody is interested.

I will go back a bit to tell you that I was doing okay managing my lyme disease, which I was unaware I had, until the shots began. Little lumps formed on my kneecaps, and dark discolored patchy rashes were visible on the inside of both knees.

Increased connective tissue pain radiated from all

points along my spine in waves that migrated to different areas, mostly the left side of my body. Brain fog, paranoia, anxiety, heart pounding, slurred speech, heightened sensitivity to light and sound, visual overstimulation brought on migraines, nausea, vertigo, etcetera. My balance was off most of the time.

Grocery stores, malls, driving at night were all impossible to do without getting sick. Meanwhile, my children now ages 8, 15, and 17, and my husband, all with diagnosed chronic lyme disease are prone to waves of most all these symptoms and more.

Everyone of us has symptoms seemingly dependent on location of tick bite, and number of times bitten over the years.

If I were not directly aware of both sides of this vaccine issue, I would likely have had all my children vaccinated with LYMErix. Thankfully this will not be so.

My husband and I heard about the SmithKline Beecham lyme disease vaccine trial studies on a local radio station in 1995, offering 350 dollars to each participant. We never received any money, I don't recall why.

We unknowingly had been living with lyme disease for years. Tested western blot negative we received all three shots. The symptoms that followed from the second shot on has devastated our lives.

I sure would like to know if my husband is considered to be in the 78 percent effective group. He has

managed to work over the last four plus years, but not without pain and suffering ever since the LD vaccinations.

SmithKline could not find his records. He works outside every day and is a living testimony as to why no one would choose the vaccine if they knew of his adverse event, especially outside workers.

I have brought all my symptoms to the attention of both the doctors of SmithKline Beecham, and the investigative doctors involved with the study. They denied my symptoms even existed, and broke their own rules, within the written consent form.

That was not their right. When considering money and reputation they have much to lose. I can only hope the truth will prevail. Please acknowledge what is happening to others who have now received the FDA approved vaccine.

Before approval my complaints about the lyme disease vaccine seemed not to represent enough people. Unfortunately, I'm sorry to say, that is no longer true. Thank goodness I found a lyme literate doctor, and more than enough up to date information and research on lyme disease than I could fathom would be available.

This has empowered me to go back to the fact that doctors only practice medicine. A good patient is someone who learns about the disease him or herself, and then helps the doctor.

The doctor must be willing to learn about the disease along with the patient. If not up on the latest information, then behind the times. This concerns both sides of the issue, not just the ones with the most monetary values.

We live on Cape Cod in Massachussets, which is considered an area highly endemic for lyme disease. I personally believe it is an epidemic proportion now. Antibiotics have, undoubtedly, helped me to gain back some of my former self. But this continues to be a long, daily, and painfully difficult task.

I wish I were back to just living with lyme disease. This vaccine has already harmed many lives. Please do not do this to our children too.

I profoundly suggest complete termination of the LYMErix vaccine until further research can develop reliable tests, and better diagnostic tools.

Thank you for listening.

CHAIR DAUM: Thank you, Ms. Lane. We would like to next hear from Mr. John Hardy, then Pat Smith and Lori Gelbart. Mr. Hardy.

MR. HARDY: Good afternoon. I'm John Hardy, I'm 65 years of age, live in Georgetown, Delaware, and I'm retired from AT&T as a fuel engineer.

I've always been very active in playing golf, hunting, fishing, camping, traveling, and working in our garden, along with taking care of four grandchildren ages four to nine.

I have been in excellent health until April of 2000. During my physical in 1999 a discussion with my physician about receiving a vaccine for lyme disease due to my outside activities, I received my first and second shots in April and May of 1999 with no side effects.

I received my third shot on April the 18th of 2000. The following week I couldn't get out bed with stiffness in my hips, neck, ankle, knees, and couldn't close my hands to make a fist.

I made an appointment with my physician, the doctor gave me some reflon, and sexlon, and sent me in for blood work. The lab work showed no lyme disease, showed a high segregate for rheumatoid arthritis.

I asked them about the vaccine I had received, and he said he never heard of any side effects. He referred me to a rheumatologist. The rheumatologist had more lab work done, and put me on solvrex, predazone, placmanil and flexarol.

My stiffness has slightly improved over the months, but I still have stiff joints, mainly in my knees, my ankles, my hands. My latest blood work has shown no inflammation in my system now, and I was tested for genes HL4DR4 and DR2, which were negative.

I really believe that this vaccine is unsafe and should be tested further. SmithKline should also have some accountability with reversal of autoimmune arthritis.

If the FDA does not take this vaccine off of the market they need to have SmithKline relabel all packaging and educate all physicians with all the potential adverse reactions.

This vaccine should not be approved for children 15 and under until all further testing is completed. It is the first time in my life I've had to rely on, or take medication, in order to function in my daily living.

Being a better informed consumer is a right, not just a privilege. Thank you.

CHAIR DAUM: Thank you, Mr. Hardy. We call next on Pat Smith, who is up at the podium, to be followed by Lori Gelbart and Linda Scharf Lurie. Ms. Smith, welcome.

MS. SMITH: Thank you. Mr. Chairman and Committee Members. The Lyme Disease Association's mission is lyme disease education, prevention, and research funding.

So one might automatically assume were favorable to a safe and effective vaccine for lyme disease. That is certainly a valid assumption.

The Association's board consists of patients, and families of patients, all of whose lives have been personally touched by this disease, and all who are dedicated to preventing others from experiencing the physical, mental, and emotional devastation lyme disease can produce.

To that end we fund national research projects, sponsor medical conferences, and continue to work with members of

Congress, developing federal legislation, providing 125 million dollars for lyme disease research, physician education, and prevention.

I am here today because we do favor a safe and effective vaccine. But we are unsure as to whether an OspA based vaccine can meet those criteria. Since the inception of OspA vaccine trials we have heard from individuals experiencing difficulties after immunization.

The information was startling, not only because of the problems described, but also because of the parent doctors incomprehension of those problems.

At a vaccine meeting sponsored by the LDF where pharmaceutical reps were discussing how well the trials were going, I questioned, without satisfaction, the issue of these trial patient complaints.

After vaccine approval LDA received inquiries about the vaccine. Many from individuals who had received all or some of the vaccination series. Most proceeded to talk about the symptoms they developed subsequent to receiving the vaccine.

When asked if they had reported this to the administering doctor, and if the doctor had reported the adverse event, the usual response was that the doctor did not take the complaint seriously, or did not think that these symptoms were related.

Sadly none were aware of the HLA DR4 situation.

And several were in the midst of the immunization series, and did not know whether to continue taking the shots.

Some called to ask if they should get the shots if they had had lyme in the past, a question which appears to have no clear answer, particularly in light of the unreliable antibody response test used to determine who has, or who had lyme disease.

A few insisted they had gotten full blown lyme from the shots. And after further discussion indicated that they had had lyme disease in the past.

I want to share an email that I received on Monday, and this is a quote. I live in Wisconsin, I received your name from person X who told me you may be able to give me some direction. I received two vaccines in the spring of 2000.

A couple of days within the first shot my neck and higher back stiffened up severely. In a month I went back for the second shot, and asked the nurse and doctor to check for side effects before I took the second. They informed me there were none.

I took the second dose and the problem with my neck and back worsened within a couple of days. My family doctor gave me anti-inflammatories, but they did nothing.

I have tried a chiropractor, but the only relief was for a couple of hours. Never tried one before but I'm getting desperate. Then I went to an orthopedic, and I am now on anti-inflammatories again, but not helping.

He told me I have a disk that is somewhat smaller than the others in my neck, and maybe the vaccine somehow aggravated it. Prior to the vaccine I have had zero neck or back problems. I am looking for treatment somehow, some way.

I called him, he is 39 years old, he asked me to help him, he wants treatment for whatever he has.

Today you are hearing about how this vaccine has physically impacted human lives. It appears that little can be done to stop whatever process triggers some of these reactions. Or if something can be done it remains, as yet, undiscovered.

I listened to the despair and bewilderment of those adversely impacted. How can this happen from a medicine to keep me from getting sick, who can help me get better?

I can only comfort them, as I do not have any answers, and I don't know of anyone who does.

This Committee has the authority to formulate recommendations that may prevent others from potentially suffering the same fate. You can revisit the original data and research which appears to show a link between OspA and adverse reactions, and view it in light of the adverse events you've now heard about.

You can recommend further studies, you can find out why many doctors who treat lyme disease are not giving the vaccine.

The Advisory Committee on Immunization Practices recommends, under future considerations in their report on the

lyme disease vaccine, June 4th, 1999, in the MMWR, "Establish post-licensure epidemiological studies of safety, efficacy, prevention effectiveness, cost effectiveness, and pattern of use."

We concur with that recommendation, and would like to see a moratorium on vaccine administration until those studies are completed, and the results critically analyzed.

Thank you very much for your time.

CHAIR DAUM: Thank you for your time, Ms. Smith, as well.

Ms. Lori Gelbart please, and then followed by Linda Scharf Lurie, and Terry Elias. I hope I'm saying that right. Ms. Gelbart, please.

MS. GELBART: I'm grateful to have the opportunity to address --

CHAIR DAUM: No, not well, sorry.

MS. GELBART: Am I okay now? Thank you.

I'm grateful to have the opportunity to address this committee, and devastated by the circumstances that bring me before you.

Since taking the LYMErix vaccine my life has changed dramatically. Let me explain. My family and I live in Chicago, I have been married for 29 years, have two children, and am a social worker.

Most importantly, until I took the LYMErix vaccine I was a healthy and productive person. My family spends summers

in southern Maine, in an area with high lyme incidence, where we are surrounded by woods and grasses, viewing deer in the yard nightly.

Already following recommended safety procedures we decided to further protect our health by having the LYMErix vaccine. We received our vaccinations at the travel clinic of Northwestern Memorial Hospital, a major teaching hospital.

Neither the staff, nor the manufacturer's literature handed to us cautioned us about the possibility of any long term ill effects. We were given no reason to believe that LYMErix warranted different consideration than any other immunization.

My husband, 15 year old son, and I had the first two injections in the spring of '99. On May 15, 2000, my husband and I received the third shot. The very next day I experienced body aches, and on May 17th I awakened with severe pain and swelling in my hands.

I was unable to bend my fingers closer than 90 degrees to my palms. I became incapable of performing activities such as basic personal care, brushing my teeth, cutting food.

Since early June I have been constantly medicated, but I still have trouble with my hands. I continue to experience pain in other joints, such as my elbows, my knees, jaw, neck and feet, and I'm usually fatigued.

Previously I was healthy and energetic, routinely

taking only calcium and vitamins. Only after experiencing this adverse reaction did I learn that there had been concerns expressed about the safety of the vaccine, particularly related to the genotype HLA DR4, for which I have since tested positive.

This information most certainly would have enabled us to more realistically judged the relative risks and benefits of taking this vaccine.

If we had still believed the vaccine worthwhile for us, I could have had the option of genetic testing to avoid a problem, rather than in response to one.

The lack of disclosure of this information had further ramifications for our family. After I became symptomatic, my son was still due for his third injection. To determine whether he should complete his series, I consulted the chief of infectious disease and travel medicine at Northwestern.

Because the concerns about a possible genetic vulnerability apparently had not been shared with the wider medical community, this doctor believed my adverse reaction was an idiosyncratic response to the vaccine that would have no bearing on my son's health.

I then consulted a physician at Tufts, more familiar with the vaccine, who advised against giving LYMErix to my son. Fortunately Jason had not had the third shot. Imagine how awful it could have been had Jason followed my path.

It is apparent that LYMErix, an entirely optional

measure intended as a preventive intervention has harmed me physically, emotionally, financially, and has negatively impacted the life of my family.

My daily functioning remains compromised. I lack the ability, the energy to maintain my former level of activity and commitments, my ability to work, volunteer in the community, and share activities with my children has drastically diminished.

I was only trying to be diligent about my family's health. And as a result I now have a health problem for which no effective solution may exist. I am faced with such diagnostic possibilities as untreatable autoimmune disease arthritis, or an activation of a previous exposure to the lyme bacteria.

There are few acknowledged experts regarding this reaction, and no widely accepted treatments. It seems to me that when evaluating the vaccine the possibility of adverse reactions of unknown duration, having no known cure, should receive greater weight than those potential reactions with well understood treatment protocols.

My husband and I have always had great confidence in the FDA's approval of medications and its communication with the medical community. We expected that all information which physicians might reasonably need to make recommendations concerning our health would be made available to them.

We were not informed that this very group expressed reservations which were not disclosed in the manufacturer's

literature. We had no idea that there were unresolved safety issues requiring further study, and that by taking this vaccine our family would unwittingly become subjects of an ongoing drug trial.

Doctors and their patients need to be given complete disclosure of a possible risk, as well as the claim benefits. Only then can they make prudent decisions together.

We hope that others will have the benefit of all of the information necessary to make well considered choices.

This morning I was thinking about your sources of data. Last May, when the nurse at Northwestern called SmithKline to report my arthritic reaction, and to seek information, she was told that there were no problems, just anecdotal reports.

They requested no further information about me. The nurse told me that she did not find SmithKline helpful, or concerned.

I thank you for this opportunity to share my experience. Thanks for your attention.

CHAIR DAUM: We thank you for your effort, and your experience. We would like to call on Ms. Linda Scharf-Lurie next, with Terry Elias following, and then a letter will be read on behalf of Nancy Vroon by Jenny Marra. Ms. Lurie.

MS. SCHARF-LURIE: Good afternoon. My name is Linda Scharf-Lurie, and I have been asked to speak on behalf of my daughter Vanessa.

Vanessa had a pretty normal childhood and adolescence until the year 1999. She had a horse that she used for exercise and enjoyment. She had competed on him in various venues. They enjoyed jumping and dressage.

She volunteered at a therapeutic riding barn, and worked with multiply handicapped children. Her plans were to get her degree in veterinary medicine, and have a small animal practice. She held down a job at a vet's office, and loved going to work and facing the challenges there.

In the spring of that year I decided to get her the lyme vaccine. She was in contact with various animals daily, and spent a lot of time in the woods with horses. It seemed like a good idea at the time.

She had had a simple case of unconfirmed lyme disease when she was around 12 years old, and it seemed to respond to antibiotics, so I thought LYMErix would be a good idea.

My primary doctor looked over the literature, and agreed to give the series of injections. Our lives have never been the same.

After the second injection Vanessa complained of ankle pain. I took her to an orthopedic surgeon who couldn't find anything wrong at that time. We sent her for physical therapy and gave her medications. She made the best of it, and never really got much better.

She had vague complaints about her joints bothering

her, but again she kept plugging along. She developed flu-like symptoms, a rash, and woke up on October 31st, 1999, with peripheral blindness.

She was having terrible muscle aches and joint swelling and pain. We went to many specialists. She had a spinal tap, an MRI, Gallium scan, multiple blood tests, including PCRs for lyme, all negative.

Finally we decided to test her for HLA DR4 and lo and behold we had a positive. We also had a positive ANA.

To this day she continues to test negative for lyme, MS, lupus, Kroen's disease, and all of the other autoimmune illnesses that our doctors assumed were the possible cause.

There is no history of juvenile arthritis in either side of our family. Her arthritis just kept getting worse, even with treatments of anti-inflammatories, and all of the arthritis medications on the market.

She spent her entire senior year at home, too ill to even walk through the hallways, and put in a full day at school. She missed her senior prom, and any social activities that a normal senior in high school participates in.

Her horse could not be exercised, or jumped by her, for a very long period of time. We have taken Vanessa to many specialists in the New York and New Jersey area. They have no explanations for this sudden dramatic change in her health, except the probability that she had a reaction to LYMErix, which somehow

caused an autoimmune reaction because of the body's exposure to OspA.

I'm not as knowledgeable as this distinguished panel of experts that I speak to, today. But I know one thing with all of my being. It was LYMErix which somehow had this devastating effect on my 17 year old child.

I think you have all considered that possibility before today. Maybe after today you will think it is more than just a possibility. You will see that this drug can have some long-lasting dangerous side effects.

Just remember, I have been told this by many a doctor in the last year and a half. They can treat and often cure lyme disease, but they cannot cure an autoimmune arthritis.

This is an 18 year old who will never again be able to run to catch a bus, jump her horse with abandon, her life will be forever changed by LYMErix. Please consider this very carefully when making your decisions about continuing keeping this on the market and giving it to children.

CHAIR DAUM: Thank you very much, Ms. Lurie. Ms. Elias, then a letter to be read by Ms. Marra followed by David Weld.

MS. ELIAS: You had it right the first time -- Elias.

CHAIR DAUM: Elias. I'm sorry.

MS. ELIAS: That's okay. I'm a health care

professional licensed in the State of Maryland. I'm also a survivor of Lyme Disease. I am also a recipient of LYMErix Vaccine.

I'm not real sure how many people have received the vaccine. If you haven't I challenge you to. Knock yourself out. I'll give you my third dose. It's in my refrigerator. Anybody want it? I don't.

I survived Lyme Disease by sheer determination. I stand here today by shear determination and a good dose of Arthrotac.

They told me I didn't have Lyme Disease. They told me my child didn't have Lyme Disease. When I presented to my doctor any possibility that I had any problem from the LYMErix vaccine, she jumped down my throat -- literally. I left that office in tears because the HMO's, number one, didn't want to pay for my first two shots.

Number two, they don't want to recognize it. They don't want to get involved. Because you know what, they just might have to do a little more paperwork. And then they may have to say you know what, we really shouldn't have given you that shot the day you walked into our office with a flaming infection from a tick bite that was bigger than the size of my hand.

But you know what, I was told that it was totally safe. I don't think so. I looked through any FDA file I could find. I combed Smith Klein & Beecham's files, anything, any kind

of medical information I could get my hands on.

Dosage calculations, contraindications, you name it I did it. There's absolutely nothing. And I'd like to question something a lady asked before. Have you changed any information that you're giving to the public? No you haven't changed a thing.

They're still giving the vaccine. There is no information in any of it that says, do not give it if you have a current infection. My doctor told me it was totally safe. No it's not.

I was almost going to get it for my 18-year old daughter who now has Lyme Disease, that I kept telling them that she had. Not on a bet. I'll take her to any Lyme Disease literate medical doctor in the world before I would ever consider giving her that vaccine.

And I work in the private duty sector. But I live in a small endemic community in backwoods nowhere U.S.A.

I drive two hours to go to work on a private duty case that I love. I almost gave up my job because everybody kept saying no, no, no, no, no, no, no, no, you're wrong. And if not for fighting back, like everybody else has, where would we be.

I challenge you all. Go to your doctor. Get your first shot. I dare you. Thank you.

CHAIR DAUM: Thank you Ms. Elias. We call next on Jenny Marra to read a letter on behalf of Ms. Nancy Vroon who apparently couldn't be here today.

MS. MARRA: No. She's in a wheelchair in New Jersey.

CHAIR DAUM: Okay. And then we'll ask David Weld and then Pat Easton to speak following. Ms. Marra, please.

MS. MARRA: She writes, To Whom It May Concern. I am unable to attend the January 31st FDA Vaccine Advisory Committee meeting due to a restrictive condition, Transverse Myelitis, resulting from the LYMErix Vaccine.

In the Spring of 1999, I decided to get the series of LYMErix shots after viewing a very convincing T.V. commercial touting the importance of protecting oneself from Lyme Disease.

I felt this would be a good thing to take advantage of since I had had numerous bites from ticks which cause Lyme Disease.

I was given the first shot of the series on April 20, 1999. Thirteen days later I collapsed completely paralyzed. Many tests at the hospital confirmed the diagnosis of Transverse Myelitis, inflammation of the Myelin Sheath around the spinal cord.

After days in Intensive Care at the hospital, I was transferred to the rehabilitation center where I spend six months. After intensive physical and occupational therapy, some mobility returned but I am in a wheelchair most of the time. My life has been drastically changed for the last 21 months.

Up to the day I collapsed, I was constantly on the

go with meetings of historical societies, community organizations, church activities, house tours, dinner parties, exercise classes, bus trips, theater outings, concerts, etcetera.

I used to wear my daughters out just telling them about all of the running around I did. I used to be a world traveler, but now because of the physical limitations I stay close to home.

I am able to live at home only with support from family and friends and a paid nighttime caregiver. For the first nine months, after coming home from the rehabilitation center, I required round-the-clock caregivers.

Prior to the LYMErix Vaccine, I was in excellent health, completely independent. I strongly urge you to take LYMErix off of the market to spare others the pain and suffering it may cause.

Very truly yours, Nancy Vroon.

CHAIR DAUM: Thank you very kindly, Ms.Marra. David Weld is next, then followed by Pat Easton and Dr. Kenneth Dardick.

MR. WELD: Good afternoon. I'm David Weld, Executive Director of the American Lyme Disease Foundation. Our organization does receive some unrestricted grant monies from Glyco Smith Klein which helps to support our overall programs and services.

Let me make it clear that it is the foundation's

policy to maintain a strict scientific standard as a basis for all information we disseminate.

The American Lyme Disease Foundation is dedicated to promoting Lyme Disease prevention, diagnosis and treatment through educational programs and services.

As a liaison between the public and medical research institutions, the Foundation provides easy access to key information that allows people to make wise health care decisions.

In particular we stress the importance of prevention and early intervention in avoiding complicated, expensive, and potentially debilitating long term illness.

Our efforts are derived from the principle that a clear understanding of lyme disease risk, and how to reduce it both diminishes the fear associated with the disease, and results in proactive precautionary behavior.

In addition we believe that lyme disease prevention techniques must target not just people, but ticks as well. As purveyors of a potentially debilitating disease deer ticks represent an almost universal threat in highly endemic areas.

Deer tick population reduction is certainly one of the cornerstones of lyme disease prevention research. To this end the Foundation support research focusing primarily on new tick control methods with potential for commercial application, and in the last year provided over 100,000 in funding for such projects.

It is our hope that a greater understanding of tick

population dynamics, tick host interrelationships, pesticides susceptibilities and other factors will enhance progress in the area of tick control.

A third approach to lyme disease prevention involves the transmission blocking method exemplified by LYMErix, the subject of today's discussion. I am not here today to argue in molecular detail the safety of the vaccine.

I will leave that task to those more directly involved in the supporting research. Let me be clear about lyme disease prevention. No one method, including the vaccine, is completely effective all the time.

The CDC, NIH, Public Health Department, research agencies and the Foundation all recommend that prevention be viewed collectively. With accommodation of precautions, including daily tick checks, the use of repellents, habitat modification and others to be taken in tandem.

I will end on this note. Science has much yet to discover about lyme disease. It does not, by any means, have all the answers. As a father of a young daughter who failed to respond completely to standard early lyme disease treatment, I have been faced with a dilemma that every parent in my position experiences, what next.

I speculated that science might not help my daughter in this case. But despite its flaws the scientific method is the best we have. It is structured to effectively

eliminate subjectivity in a controlled environment.

Any anecdotal evidence pertaining to LYMErix or any other vaccine which may be developed, until subjected to rigors replicable study is of limited value in assessing the vaccine's merit, and in determining policy relating to its use.

Thank you.

CHAIR DAUM: Thank you sir. And I hope you catch your plane. We have Pat Easton followed by Dr. Kenneth Dardick.

MR. EASTON: Thank you for allowing me to speak here today. I'm here representing my wife, Carol Sue.

My Susie is 17 years younger than I am, and until two years ago she could run circles around me, and out-think me. All that has changed.

Let me give you a brief history. In 1998 she had an operation on her back, a bad disc. But during that, and before that operation she was thoroughly checked out, head to toe, because the doctor didn't want to proceed if there was any indication of arthritis.

She had a head to toe check out, no arthritis whatsoever. She went through that operation, remarkably she was doing everything she should in that summer of 1998.

In November of 1998 we moved from the 95 beltway, 250 miles northwest to the mountains of Pennsylvania, got a new HMO, new doctors, the whole thing. That was in November. In about the February time frame both of us went in to our new HMO

and did the head to toe check out, both of us, complete physical, nothing wrong with us.

At that time it was suggested to us, since we were going to live in the woods, and work in the woods, and what have you, that LYMErix was the way to go. We both took it.

She noticed some pain off the first shot, but for her, I teased her and said, that is typical. When you get the flu shot you always get a mild dose of the flu, you know, that is you.

And she took the second shot, and immediately thereafter started all the symptoms that you heard many, many times over.

I would like to add a few other ones. She is now deteriorated, her eyesight is going. She is losing her mental capacities, too. It is a little tough. For a woman that I was worried on how I was going to keep up with as a 60 year old, it is hard for me to lay in bed beside her and hear the whimpers that she tries to turn -- excuse me.

On your reporting system, your VAERS reporting system, it took me 18 months to find it. She isn't even in your thing. We finally got to it, found a copy of it and mailed it in. I have to admit the people that phoned back were very, very cordial, very helpful, and spent a lot of time with my wife.

But your reporting system might do well in the beltway, but out where the ticks are, out in the hinterland, nobody knows about it, or they are not telling you.

Out in the sticks, and out in the hinterland the doctor, God love her, she tried everything. We have been diagnosed from everything that you ever imagined, down through lupus, tested for and come up no. Because she couldn't believe in her heart that it was the lyme vaccine because she said there is no indication -- she is upset to this day because I brought her from other sources.

And she said, why didn't they have that down there, Pat? I apologize, I'm sorry. But she is still upset because she doesn't have the information from you, she had to get it from me.

Thank you, sir.

CHAIR DAUM: We thank you, Mr. Easton. Dr. Dardick is our final speaker of the afternoon. Is Dr. Dardick here? I think probably not.

Are there other people who wish to come forward and speak for five minutes, that haven't made themselves known to us. I see one hand. Would you come to the microphone and identify yourself, please? And this will be our final speaker.

MS. BURKE: Hi, my name is Karen Burke. I wasn't planning on speaking, I have no prepared, anything to say. We are here because my husband had the LYMErix vaccine two years ago, actually a year and a half ago.

He loved hunting, always outside, we have two dogs, take them out in the woods, love to run. We are also from the Poconos mountains of Pennsylvania.

He had his own construction business, loved it, did great physical, physical work. We have two small children, a little boy who is now three, and a little girl who is 11 months old.

Anyway, he had the first vaccine in June of 1999, the second dose in July of 1999. By October of 1999 he couldn't get out of bed. Severe swelling, heat from the joints, fever, couldn't walk, couldn't peel a banana, couldn't do anything, couldn't roll over in bed, couldn't pull up the covers, had to go to the bathroom, well guess what, you are not making it to the bathroom, because you can't move to get it there.

No one can help you because they have to pull on you or move you, it can't be, they are hurting you, it hurts. It is awful, devastating, it has changed our life completely. I found out I was going to have my little girl July of 1999. Well, I guess that was God's way of letting us have a second child, because the medication that he is on, by the way he takes four medications, they are all damaging in some way to the liver, toxic.

Prednisone, which as we all know can cause osteoporosis, they are finding that now, particularly in males, from what I understand. Anyway, we are not able to conceive any more children until he is off these medications.

Will he ever be? You know, the standing joke is, I love to kid around, right now I wasn't planning on being up here,

I didn't realize I could speak. If I knew it, I would have been prepared. I am like a nervous wreck, you can hear it in my voice.

But my standing joke with him is, honey, at least when our kids are big enough and by that point you will probably be on a wheelchair, and you will get us on the rides quicker. Well, you know what, that is a joke, it is not funny, but you have to have some fun in your life.

And it is not anymore. He lost his business, he has no more construction business, done. Pretty much a desk job. Thank God he has a job, thank God I have a good job.

The point is life has changed, and is it ever, ever going to be the same? I truly, truly believe it came from the LYMErix vaccine. As someone said before, I mean, I know it is not for me to ask you guys questions. How many of you people have it, the vaccine, how many of you people would give it to your loved ones?

And if you did, you wouldn't be sitting where you are right now.

I really, really believe it came from LYMErix vaccine, just as everyone else has said. Our life has been turned upside down. Fortunately it is not something worse, fortunately it is not something that is going to kill him, or at least we don't know that it is.

So I just urge you to consider at least change the labeling, at least let people know that they have genes in their

body, that if they carry this gene, in lay terms, they can go ahead, get tested to see if they have this gene before their life is ruined.

My husband does have the gene for rheumatoid arthritis. Never knew it. Perfectly healthy, healthy individual. Not any more, completely, completely changed. Functional after three or four o'clock in the afternoon? No. Where is he? On the couch. Is he sleeping? Yes, he is sleeping he is a mess. Two little kids, can't play with them.

The point I'm making is it is an awful, awful thing. If you went through it, all I can say is it is devastating, and it is awful, it has turned our lives upside down. Please consider not giving it to small children, or to anybody else, because do you guys finish your study, how many more people are going to be affected, how many more people are going to have this problem?

There is just too, too many to say it is coincidental, it is not. That is all I have to say. I'm grateful I had the opportunity to come up here, I wished I would have called and made arrangements to speak.

I'm done being a nervous wreck, I'm glad I got my point of view out. That is it, I'm going to go sit down and get some water.

CHAIR DAUM: And thank you for taking the time to share your thoughts with us.

I have to tell you, sitting up here as a physician, that the stories and the thoughts that were shared with us this afternoon can't help but be profoundly moving.

And I can assure you, on behalf of the committee, that your views, your thoughts, your energy and time taken to share your ideas with us today, will be taken into account in our discussion and deliberation.

I would like to now take a ten minute break, and then we will begin committee discussion. Thank you.

(Whereupon, the above-entitled matter went off the record at 3:08 p.m. and went back on the record at 3:24 p.m.)

CHAIR DAUM: Welcome back. We are now going to have the -- everybody sort of settle down, please. I know it has been a long day. We will try to get this done quickly so that we can get people on their way, and back to homes or activities.

The Committee will now deliberate the issue that is put in front of them by our colleagues at the FDA for discussion. And in this instance we are not going to have a direct vote on anything, but we are going to address this question, this issue.

Please discuss the safety data and the plans for continued safety evaluation of the lyme disease vaccine. Appended to that, I've just been told by Dr. Midthun, is that comments about what might or might not be done to the package insert, or the labeling are also welcome during this session.

What I would like to do is to first have those members of the committee that wish to ask clarifying questions, or raise points, to feel free to do so for a while. When we get the sense that most of the points have been raised, I will then like to hear this issue of the FDA's spoken to by everyone at the table.

So we will begin by people who want to raise points that have come out of today's session, and we will try and get some discussion going on them.

DR. DATTWYLER: I will raise something.

CHAIR DAUM: Okay, then Ms. Fisher. Thank you.

DR. DATTWYLER: On the point of serologies, the original serology recommendations from the CDC panel were not in reference to western blots, they were using an infectious disease principle, acute and convalescent serologies.

And the idea was a standard rise in titer could be indicative of acute disease. And I think there was some misconception there that that was in reference to western blot, it was not.

The other thing is that the scientific basis of the CDC recommendations, as far as serologies, is not solely based on just the Dressler-Steere study. But, in fact, there were additional studies carried out by members of the CDC Advisory Panel, and CDC itself.

So that has been validated through a number of

different scientific studies.

CHAIR DAUM: Are you raising, clarifying issues with respect to understanding serology for us?

DR. DATTWYLER: Yes, that is all I am doing. And I can also say, as a member of that CDC committee, that the vaccines were never discussed in serologic meetings. So that there was no forethought about vaccine trials. We were solely concentrating on serologic issues at that point.

CHAIR DAUM: Thank you. Ms. Fisher, you had your hand up?

MS. FISHER: I had a question after Dr. Elkins presented, and I would sort of like to ask it to her, and also to SmithKline Beecham.

In light of the findings by Dr. Shell that at higher concentrations OspA protein there was an effect. The OspA vaccine preparation contains 30 micrograms of OspA protein, I understand. And the mice that were injected in the SmithKline Beecham study were injected with one microgram of OspA.

My question is, could the concentration of OspA protein affect the findings of studies in the animals?

CHAIR DAUM: Dr. Elkins has just come into the room, and might not have heard your entire question, Ms. Fisher. Would you mind repeating it for us?

Dr. Elkins, this is a question for you and for the sponsor.

DR. ELKINS: I am sorry, what was the question?

CHAIR DAUM: Why don't you repeat the question, please?

MS. FISHER: The OspA vaccine preparation, I understand, contains 30 micrograms of OspA protein. And the mice that were injected in the SmithKline Beecham study, I think you said they injected one microgram of OspA. And I was wondering, in light of what you talked about with regard to Dr. Shell's work, could the concentration of OspA protein affect the findings of these studies?

DR. ELKINS: Well, I won't attempt to address the question from the SmithKline experiments with the mice. In the Wisconsin study they used three doses, 30 micrograms, 60 microgram, and 120 micrograms, 30 micrograms is the adult dose.

And, of course, a hamster is much smaller than a person. The dose response in that study was not very well characterized. They did report that there was less of an impact on joint swelling after infection at the higher dose, the 120 microgram dose than at the 30 or the 60 microgram dose, which I think is probably counterintuitive.

Clearly there could be dose related effects, but how you would relate those between hamsters and mice, and adult vaccination, is very difficult.

CHAIR DAUM: Thank you. Does someone from SmithKline want to deal with that? Is Dr. Lobet here?

DR. LOBET: We believe that the use of such a high dose in hamsters is exaggerated, in a way, because it would represent something like, if you compare the body weight, 504 higher concentration than what you would use in humans.

Further, when injecting the hind paws, you are going to exacerbate an inflammatory process, because in this location it is known that an inflammation would take place. I mean, this site is prone to severe inflammation.

We use one microgram in our studies because we find this more relevant to the human situation, and closer to the human situation, as you have seen in the past, using one microgram of OspA was the dose to approach the immune response seen against OspA in humans.

And we thought using one microgram of course would reduce the body weight, the concentration, as compared to the hamster study.

MS. FISHER: It is interesting that there is no dose adjustment for, you know, one day old infants versus adults in hepatitis B vaccine, so there is no dose adjustment there.

DR. ELKINS: There is probably another point that should be reiterated about the hamster study.

CHAIR DAUM: Go ahead.

DR. ELKINS: Which is that the recombinant OspA used in that study was produced by the investigators, it was no the LYMErix vaccine. And the investigators stated that it was a

non-lipidated version of the protein.

Although that characterization data was not included in the paper, and the technique used to create the protein would have, from the description given in the paper, been just as likely to produce a lipidated protein. So there is some unanswered questions of exactly what the injected recombinant material was, and how that might compare to the LYMErix vaccine itself.

DR. SNIDER: Could I just ask a follow-up? Did they use an adjuvant --

DR. ELKINS: Yes, they adsorbed it to one percent alum.

CHAIR DAUM: Dr. Griffin is next.

DR. GRIFFIN: I just wanted to comment, from an immunologic point of view we don't usually adjust doses in the same way that we adjust drugs, by weight. I mean, frequently, Ms. Fisher is right, the same amount of vaccine is given to a very small person, as to a large person. The same way with animals.

DR. LOBET: Sure. But in the case of mice we know that --

DR. GRIFFIN: In the case of mice.

DR. LOBET: In the study in the mice we know that we get the same immune response in humans with using one microgram.

CHAIR DAUM: Dr. Myers, then Dr. Ferrieri please.

DR. MYERS: I have two questions. The first one I would like to ask Dr. Ball. I know with VAERS it is very hard to make a comparison of apples and oranges, and so on.

But there are 322 cases reported of arthritis, arthralgia, or arthropathy. And there were 44 that reported a severe musculoskeletal diseases. And the manufacturers told us that 1.4 million doses of vaccine have been administered.

And I realize that the comparison I'm going to ask for is not a valid one, but give us a sense of perspective.

Could you tell us of another vaccine that is directed at the same sort of age group, what type of VAERS report do you get in the same areas? For example, hepatitis B illuminating the pediatric administration, or some other vaccine?

Is there some way you could give us a feel for whether 322 and 44 is more than you would have expected, or DT would be another vaccine.

DR. BALL: I can't give you the numbers, I don't have that information. But I can tell you that we did look at reporting rates, where reporting rate is the number of events divided by an estimate of the doses distributed, and compared the reporting rates for various coding terms for LYMErix with hepatitis B vaccine given to adults, and also flu vaccine given to adults.

And what we see there is that for pretty much every coding term the reporting rate is higher for LYMErix. And then if

you specifically look at the coding terms for joint related symptoms, the relative reporting rate, which would mean the ratio of the reporting rate for LYMErix, compared with the reporting rate for, say, hepatitis B vaccine in adults, is also higher, and it is a little bit higher than you see for non-specific coding terms, such as flu syndrome.

But, as you are saying, there are a number of caveats to those comparisons, specifically we know that for newer vaccines there is more reporting, and that is suggested by the higher overall rates for LYMErix.

We also know that media reports can influence reporting differently, for different vaccines. And we know that age and gender differences of vaccine recipients can also influence reporting. And although we have tried to account for that by just looking at reports in adults for hepatitis B and influenza, we don't have age and gender distribution for the actual vaccine recipients.

And it is probably different for people who receive flu vaccines, probably older, and probably a little bit younger for people who receive hepatitis B vaccine.

So, overall, as a result we can't really conclude that an increased reporting reflects a causal relationship between the vaccine and the events for which the reporting rate is increased.

But it does focus our attention on those events.

Now, in this case, we were already focusing on the arthritis reports because of the theoretical concerns. So it essentially reinforced that.

CHAIR DAUM: Thank you.

DR. MYERS: The second question I had really had to do with a post-marketing studies, and only 3,600, approximately 3,600 cases enrolled to date.

And given the enrollment problems with the fact that 1.4 million doses of vaccine have been distributed, I wondered what the manufacturer's plans were for trying to rapidly address the problem of getting the data.

CHAIR DAUM: Yes, I would like to hear the answer to that, as well. Does someone from the manufacturer want to take that on? Dr. Kahn.

DR. KAHN: I think this is a good time to call up Dr. Platt, in fact, to talk about that specific issue, if I may. And at the same time I think it is fair to say the uptake of the vaccine is low, and we've often pondered this ourselves.

And there are a number of factors that we think of, is an adult vaccine a personal choice vaccine, it is restricted by geographical and, indeed, seasonal use.

And adults, unlike pediatric vaccine, where there are recommendations and plan visits, is quite a challenge to actually get the word out that this is available, and have adults come in of their own volition, and you see that.

And I think the negative press must have caused the attitude. It is an obvious thing. So maybe I can ask Dr. Platt about the plans for the future.

DR. PLATT: Part of the resolution is the addition of additional managed care organizations to this study, which is already in train, so that the cohort is actually two to three times larger than we were able to report.

That is, we will have the data from the beginning of 1999 for all three of the HMOs by the latter part of this year. I do think that it is important to recognize sort of what will exist at that point, because it is because the information you get increases more or less as the square root of the number of cases.

Roughly speaking 5000 cases gives you about half the information that 25,000 cases will get. That is not to minimize the importance of getting as much information as possible.

But if, for instance we were at the end of three years of recruitment to have twelve and a half thousand cases, half the size we were expecting, we would have something on the order of 80 percent of the information that would come from a 25,000 member study.

So there really are, I think, two ways to approach this. One is to try to get the additional information that is already entrained, available as soon as we can. And for us that means later in this year.

And then I think to evaluate what we see in that. I think there would be -- I personally would have a very different response to seeing no excess in the immunized group versus a modest excess that we can't distinguish from random noise.

And we should be there, I think, by the end of this year. That would also, I think, be a time when we could evaluate the prospects for getting other population based sources of information that might be able to contribute to this, either to this study, or a companion study.

DR. MYERS: Just a final question and I will be quiet. I take it from the answer, then, that the manufacturers are not planning on other studies, it is a one study post-marketing plan?

And are there other investigators that are going to increase the data base? Or is --

CHAIR DAUM: I'm not sure whether you are talking about -- are you expressing dissatisfaction that enrollment in this study is going slowly, or are you asking --

DR. MYERS: Well, I was asking if there were going to be other studies in addition, because this one is going quite slowly.

DR. PLATT: I don't mean to speak for the manufacturer on this. I will tell you that I have looked, fairly diligently, for potential collaborators who could contribute.

DR. MYERS: I didn't mean it critically.

DR. PLATT: No, I wasn't taking it critically. I'm just telling you that as an investigator who would like to see the study progress more quickly, I have essentially on my own initiative, but with the knowledge of the sponsor, enquired of other potential participants.

And I'm unaware of any at this moment. It may be that by next year others that could participate would be willing to do it. But I have talked with, I think, all of the investigators who would be in a position to do this kind of work.

And they fall, basically, into two categories. Those who work in environments where lyme vaccine is not used very much, and those who just can't take on the commitment of doing the study at the moment.

DR. O'FALLEN: I am not sure I agree with the rather optimistic expressions of the kinds of power that we have after getting only half, or perhaps even only a third of the originally prescribed studies.

The standard error of an estimate is reduced by a factor of two only if you increased the sample size by a factor of four. So you really, I think, overstated what we will have available if we don't get a fairly substantial proportion of the original target.

And I'm not sure, as I said earlier this morning, that I believe that you will get even as big a group as you think you are going to get, especially from the Minnesota group.

CHAIR DAUM: Dr. Coyle, did you have your hand up? Thank you, Dr. O'Fallen.

DR. COYLE: I actually had a question, and I was wondering, in the cohort study do you feel very confident that the problems similar are akin to what the patients were testifying to here, would clearly be picked up?

I'm wondering about the possibility of including something like a new pain syndrome to make sure that it is picked up. Do you feel confident that all of these patients that if they were in an HMO cohort, your HMO cohort would be picked up, would be detected?

DR. PLATT: My belief is that we would. We are providing to FDA a tabulation of all of the ICD9 codes that are submitted, not just the ones that are in that group that are called arthritis, and musculoskeletal.

So in the event that these syndromes would be coded outside those ICD9 codes, we would be able to see that signal, and FDA reviewers would see it as well.

So I expect that the kind of problems that require many visits to a physician for that problem are the kind that would likely show up as signals in a claims data base, even with all the problems that the claims data bases have.

Could I just return to the prior comment? Because I didn't mean to disagree with your statement about power. And I really do believe that recruiting the full cohort would be a

desirable thing to do.

I just want to be sure that we have a common understanding that the information we received is greatest for the first cases, and marginally less for the later cases that are recruited.

We have preliminary counts from Minnesota, and I think that I'm giving you a fair estimate of the cohort size that we will have by the end of the year.

CHAIR DAUM: Thank you. Dr. Ferrieri, Dr. Estes, Dr. Diaz, Dr. Goldberg.

DR. FERRIERI: Thank you, Dr. Daum. A couple of brief comments, and then some sort of suggestions with, hopefully, response from the sponsors.

I chaired this committee in May of '98 when you presented data that led to our recommending to FDA that the product continue in the process for licensure.

And you have heard everyone say that we had many reservations, and they are in all the documents that people have received. So I will not reiterate them.

But they have surfaced today from many people, and FDA knows what they are. And I think, honestly, that the sponsor has attempted to obtain data that would address our concerns.

But here we are, two and a half years later, and really aren't much further along. So the uneasiness that some of us had then, and there are at least two people at the table,

perhaps other than I, who did participate on that occasion.

I think that the uneasiness then is duplicated today, because the same questions persist. And I'm worried that the clinical data are not going to be forthcoming, that they may be inconclusive, that is worse case scenario.

And because of the low uptake in receiving the vaccine, that we may not be able to arrive at that faster.

Now, it is quite possible that this is, basically, a reasonable vaccine that fills a niche. And at the time, you know, within five years, two and a half years ago, there was great lay pressure and enthusiasm for having this licensed, for the lyme vaccine to be licensed.

So the expectation was that we would have those knowledge gaps filled, perhaps. But if we can't then I think we have to get back to the drawing board and try to attack this from a basic science point of view, and we need more basic research to help understand OspA, the gene, domains of the gene, perhaps.

I don't pretend to understand whether the epitopes for protection are different from epitopes that may regulate unfavorable reactions, and arthropathy, for example, or reactivation of something.

And, lastly, we might learn from the hamster model, perhaps, if we could manipulate the end result protein from a genetic point of view, and perhaps use the hamster model, we might be able to get to some of these questions that would be applicable

to the human vaccination safety issues.

And earlier today we talked about the mice, and the lack of data to examine the administration of the OspA after vaccination. I'm sorry, the OspA after experimental infection.

But from the hamsters we've learned that the reverse is very intriguing as well, and that is OspA vaccination followed by experimental infection, that is out there for all of us, if we are exposed to the borrelia bearing tick.

So I would like you to seek out and get right to your corporate hearts and examine, how strongly you are attached to this vaccine, do you want it to be out there in the market? Because it is like a stock that is losing interest, you know, is this going to be the fate of Amazon.com?

I hope not, because you've put a hell of a lot of money into this. But you need to know how far do you want to go with it, how far are you prepared to go to unravel some of these very basic questions in addition to safety issues in human vacinees.

CHAIR DAUM: Thank you, Dr. Ferrieri, I think that was a very helpful comment for us all to hear.

I would like to go on with Dr. Estes next. Thank you.

DR. ESTES: I wanted some clarification about what studies, if any, are actually ongoing to look at the association between the HLA type and potential reaction to this vaccine.

We were told this morning that the cellular immunity studies that have been completed were exploratory, and they were of limited power. And it is not clear to me that Dr. Platt's studies are going to address that.

Are there other studies that we don't know about that are planned, that are ongoing?

CHAIR DAUM: I'm going to ask the sponsor to address that, but I would also like to hear from FDA folks as to what they know that is going on that may have nothing to do with the sponsor.

But let's hear from the sponsor first.

MS. HOWELL: I'm Barbara Howell from the clinical research unit for Glaxo SmithKline in the U. S. And I just want to make one point with regard to the HLA typing pre-licensure.

You've heard, this morning, that there were basically two studies in which HLA typing was prospectively done. One of them was the lyme-008 study, which was the pivotal efficacy trial in which the HLA typing was done in conjunction with the cellular immunity study in a subset.

And as you heard, and as everybody agreed this morning, those studies were largely exploratory. They don't support any association between arthritis and HLA type, but they don't definitively refute.

The point I would like to make is that in addition

to that we know that in a large efficacy trial which involved more than 10,000 subjects, half vaccinated, and half placebo recipients, that study was prospectively designed to look at a comparison of musculoskeletal events, neurologic events in vacinees, as compared to placebo recipients.

And that based on the prevalence of the HLA DR4 allele in the general population we know that up to 30 percent of individuals then, both vacinees and placebo recipients, would carry the DR4 allele, and that there was no increase in musculoskeletal neurologic events.

We have been in discussions with the investigators of a phase IV study to explore whether or not we can look at HLA typing in the context of that study. We were concerned about delaying the start of the study proper because of considerations having to do with logistics.

One of the proposals would be that we could potentially look at HLA typing in vacinees who were exposed, and unexposed, who developed incident arthritic conditions, but perhaps do that only if we do determine that there is an excess in the outcomes of interest, and that would be done further down the line, in the context of that trial.

Otherwise we do not have any other plans for HLA typing in humans.

CHAIR DAUM: Thank you, Dr. Howell. Would someone from FDA like to speak to, do they know whether anything is going

on in this area? Dr. Ball?

DR. BALL: I just wanted to repeat what I said during my presentation, that the FDA is sponsoring a study. Initially it will be a survey of people who have reported joint problems to VAERS, and then once we obtain complete information on those cases we will identify arthritis reports and conduct a case control study comparing people who report arthritis after lyme vaccine, with people who report arthritis after other vaccines to VAERS, as well as people who report adverse events, other than arthritis after LYMErix to VAERS.

And in that study we intend to do high resolution HLA typing of all the cases and controls, and to compare the prevalence of rheumatoid arthritis associated HLA alleles in those groups.

We also propose to look at t-cell reactivity to OspA and LFA1 in those -- in the cases in the control groups.

DR. FERRIERI: How many numbers do you project? I was confused, Dr. Ball, about this case control study. What are the projected numbers?

DR. BALL: Well, we know right now that we have about 133 reports of arthritic conditions in VAERS. We don't know how many of those will actually pan out to be true cases of arthritis.

So once we do our survey and obtain that complete information we will be able to identify the number of cases, and

then we would match that with the different control groups.

My sense is that we will have something less than 100 cases. And so that the study is likely only to detect a fairly large effect at points present.

CHAIR DAUM: Does anybody know whether the -- thank you, Dr. Ball. Whether the NIH is interested in this? Because it sounds like it is some pretty basic immunology and microbial genetics to be done here.

And I wonder, does anybody know whether that has been declared to be a funded area for someone to be working on? If not we should probably get a sense from the committee that we think it is a pretty important knowledge gap, and that we would like -- we appreciate the efforts of the sponsor and FDA, but would also like NIH to get to work on this as well.

Dr. Diaz, I think you are next.

DR. DIAZ: Dr. Ball answered one of my two questions, so thank you, I might come back to you later with a couple of other questions about the case control study.

But the other question that I had was in regards to the studies that are ongoing now, and your large HMOs. And we've had discussions today, in particular, and I likewise am concerned about the utilization of ICD9 codes, and what gets coded, etcetera.

I was just curious if any of the HMOs that are participating are going to participate in this study, by any

chance, have any computerized data such as chief complaint, or triage data that could be looked at in addition, to try and mine for effects, perhaps, that may be associated with vaccination?

DR. PLATT: HMOs are largely quilts these days, made up of a variety of delivery systems. Harvard Pilgrim includes a multi-specialty group of about 250 to 300,000 that has a fully automated medical record.

And so those individuals are included in the data that I showed you. There we are not limited to the number of -- to the number of diagnosis allowed on a claims form. We search all the diagnosis that are used there.

So we have, essentially, the full automated medical record in that case. And health partners also has a more limited, a fraction of the health partners population I understand also has full, has automated medical record capabilities.

So for something on the order of 20 percent of the population that we are describing, there is more than just billing data that is available.

DR. DIAZ: If there is, that data might be useful to look at as a subset. Just to compare chief complaint and final diagnosis in terms of validity.

DR. PLATT: So we can subset that out, understand that we are, at the moment, looking at serious conditions as manifest by hospitalization there are very few events. So it will still be very few events if we look at a subset.

DR. DIAZ: I'm sorry, I misunderstood. So the data that you have, in terms of full medical record, is only for hospitalized patients?

DR. PLATT: No, I'm sorry, I didn't say that well. We do have, now, the full medical record data is only for the ambulatory care. That information is included in the data we gave you, and we can subset that out.

DR. FERRIERI: I'm from Minnesota but don't know health partners well enough to know how far along they are. But it would be my assumption they have a centralized data base now from all of their hundreds of clinics you would have everything feed into a central center, then, Rich?

DR. PLATT: We have access to all the data that health partners has, centrally. But health partners has a substantial part of health partners, I understand, about two thirds of it, is physicians basically in separate practice who don't have automated data.

So I think they too have sort of a two-tiered data quality configuration, in much the way that Harvard Pilgrim does for 20 percent of our population we know enormous amounts of information. And for the rest we have billing data, and my understanding is something like that is true for health partners.

CHAIR DAUM: Dr. Goldberg, please.

DR. GOLDBERG: Dr. Platt, the question that you just answered about the 20 percent of the population with complete

data --

CHAIR DAUM: Would you speak into the microphone?

DR. GOLDBERG: The 20 percent of the population with complete data would speak to the kinds of questions that were being asked this morning for a substudy to compare the diagnosis there with their billing diagnosis, and then compare that to the total population.

You also said that 14 percent of your population turns over yearly at the Harvard Pilgrim. From the kinds of discussion that we heard this afternoon, if the complaints, or if short shrift is given to the complaints, these people might be more likely to leave the system.

I mean, have you thought about -- you talked about the fact that you would be unlikely to miss a diagnosis, a code that was recurring, or if somebody kept coming back, even if it wasn't in the first few visits it would be in a later visit.

If the patient was to be told this is not something we are going to deal with, which I'm hoping doesn't happen, you could lose that patient to the system, completely.

Have you got some ideas about how you might address those sorts of issues?

DR. PLATT: I can say, as a general phenomenon, the member satisfaction data suggests that he members, in fact, by and large are very satisfied. And the turnover is actual bimodal. That is there is much more rapid attrition for new members, and

then much lower attrition for members who have been -- for individuals who have been members for three years or so.

Much of that change in membership has to do with employee's decisions about the insurance company --

DR. GOLDBERG: I understand that.

DR. PLATT: So it is a complicated business to understand. And I think what we can do is provide basically sort of a life table analysis of the duration of membership after immunization, and even the number of visits after immunization, which I think would give us some sense of whether people are leaving soon after they are immunized, or whether they continue to have encounters for other diagnosis.

DR. GOLDBERG: I have a question for the sponsor. Given that the vaccine is --

CHAIR DAUM: Dr. Goldberg, I have a number of names lined up here, but why don't you go ahead. But let's try -- Dr. Goldberg will go, then Dr. Stephens, Dr. Luft, Dr. Manley.

DR. GOLDBERG: For the sponsor. I mean, given that the vaccine is really not out there massively, have you considered some kind of registration with each immunization so that you had developed a registry of vaccinated individuals who then might be able to be used for case control study that could be completed more rapidly than the kinds of things that you are involved in now?

DR. WEADON: While we are deciding on someone else

to respond to this, I want to come back, I will answer that question, but I also want to address an issue that was raised just a little bit earlier.

And that is that we are no further along than we were two years ago at the time of licensure. I think we need to remember that as Dr. Francoise Meurice, and Dr. Bernard Hoet have shown, our overall control safety data base has doubled from the time of licensure.

So we've added -- we've had a doubling of that control safety data base. Additionally, as you've heard from Dr. Platt, we've enrolled in the phase IV study, albeit not at the rate we would like to see, some 2,000 enrollees, actually 3,000, we don't have all the data for that additional.

We've heard from the post-marketing adverse experience data base that that, given the considerations outlined by Dr. Ball, is one that is aggressively and continually reviewed.

So it is not that we have not progressed from where we were two years ago, we have progressed. And the questions have been asked, over and over again, and the answers have, to date, been consistently the same.

That the adverse event profile that we saw pre-licensure, have been corroborated in all of the various domains in which we've asked the question.

However, the effort has not stopped. We will continue to look very carefully at how we can enhance the accrual

into the phase IV study. We have not, to my knowledge, looked at a patient registry situation. And my colleagues here are shaking their heads, that that is not something that we have considered to date.

So that is not something we have discussed with the agency at this time.

CHAIR DAUM: Thank you. I think that you are hitting on an important issue that the committee is shortly going to be asked to address. And that is that in their view, the committee's view, do they feel that the safety profile at the time of licensure, and the safety profile now, have changed in a way that should concern us.

And has it, or hasn't it, or do we know? And I think those are the kinds of data or opinions, at least, that the FDA would like to hear from us about. And there will be a couple more things that I will charge you with shortly to comment on.

But I would like to hear from Dr. Stephens, then Dr. Luft and Dr. Manley.

DR. STEPHENS: I would like to follow up on a point that Dr. Ferrieri raised a minute ago about basic mechanism of this vaccine, which I still don't understand.

Can you clarify, can the manufacturer clarify the issue of how you think this vaccine works? The data suggests that it neutralizes OspA in the tick as the basic mechanism. But I have trouble with that particular, that that is the only

mechanism.

And secondly an issue we raised this morning about the lipo protein component of this vaccine, what is the lipid, can you clarify that, are there any evidence that antilippid antibodies, cartiolithen, for example, are produced in response to this vaccine?

PARTICIPANT: To answer your second question we have no evidence of that, indeed, we don't know that.

DR. STEPHENS: I'm sorry?

PARTICIPANT: To answer your second question we don't know that.

To answer your first question you mentioned --

DR. STEPHENS: I'm sorry, you haven't looked at the lippid that is contained in this vaccine?

PARTICIPANT: If we have looked in the lippid, at the lippid?

DR. STEPHENS: What is the lippid portion of the protein.

PARTICIPANT: Those are palmodic acid at the interminus of the protein through its natural processing. This is a mechanism that is very common through, in many bacterial proteins. This is during the process.

DR. STEPHENS: What is the lippid component of the vaccine, structural?

PARTICIPANT: Structurally those are palmodic

acids, three palmodic acids at the end of it.

DR. STEPHENS: And the e coli vector puts those on in the same way that borrelia does?

PARTICIPANT: Yes. This post-transitional modification is something that is common to many bacteria.

DR. STEPHENS: I appreciate that, but there is a lot of difference in how bacteria may attach certain fatty acids to their proteins.

PARTICIPANT: I agree. We have checked, and the profile, the lippid profile of the protein producing e coli is similar to the one observed in the protein produced by borrelia.

DR. STEPHENS: So the lipid portion of the protein is the same as that produced by borrelia?

PARTICIPANT: Yes.

DR. STEPHENS: Now, the follow-up question has to do with any evidence of antilippid antibodies produced by the vaccine.

PARTICIPANT: We will look at that.

CHAIR DAUM: You've not looked at that?

PARTICIPANT: No. The first question you asked was about the mechanism --

DR. STEPHENS: The expert, presumably the tick, the OspA in -- and that data, I think, goes back to the '92 study looking at immunofluorescent data in ticks with or without the vaccine.

Is there any other follow-up data to talk about how this vaccine works?

PARTICIPANT: Well, all the more recent data still confirm that the mechanism, as it was described at that point, and you have to take into account two aspects. The first is that OspA is expressed when borrelia is in the midgut of the tick, that is one.

And so when the tick ingests some blood, or some serum containing anti-OspA antibodies, it could be killed, borrelia would be killed within the tick midgut.

This is one point. Now, all the clinical experiments that have been conducted since then, using direct challenge experiments, show that you will clean the ticks from their borrelia infection when they feed on animals that have been immunized with OspA. Does this answer --

CHAIR DAUM: I think so. We are going to move on. There is three more people lined up on the question list, and then I'm going to begin the process of eliciting some summation comments from the committee., based on this discussion.

Dr. Luft you are next, then Dr. Manley and Dr. Diaz.

DR. LUFT: I just wanted to comment about the lippidation. That the actual lipoprotein, the fact that it is lippidated does almost act as a mitogen, and it gives a whole host of other -- so, I mean, that is --

In a way I feel like I'm almost in a twilight zone when we are talking about surveillance and these adverse events, and I forgot the name of the -- one of the vice presidents from Smith Kline.

What disturbs me is that in the SmithKline presentation there were 950 adverse events. There was a nice presentation of that. And this afternoon we heard testimony from 20 individuals of 20, of approximately 20 people who had very significant adverse events.

And the disconnect for me is I'm hearing that, and I'm seeing that data, and I don't see any reflection of one to the other as if we were in two different universes.

I'm not ascribing what the validity is to these complaints. Certainly I was moved by it. But the fact of the matter that it didn't even enter into the discussion, or into the charts, or the tables, is disturbing.

And there is some problem in the actual, the adequacy of the surveillance that is currently going on, in that we are not seeing that data in the company's presentation.

And it goes back to my original point about the ICD codes. I think in this particular situation, where you may have an Amazon.com, you have to be able to get assurances, you have to be able to feel secure, you have to make sure that actually there is a very active surveillance system that is going to out, that is going out and actually pulling in these types of cases.

And I think that that is something that we have to consider. I don't think the idea of a passive type of system, or a system that is going to take three to five years to kind of figure out whether we had an adequate power, or whether we had an adequate input of the right information, or whether we were -- whether we cast a wide enough net will really be adequate.

And I invite the sponsors to give me some insight as to why there seems to be this discrepancy. But, in a way, I think I'm just restating the obvious. This is -- I mean, I can't --

DR. MANLEY: That is my concern, specifically, so if I can speak now, because it is the same question.

CHAIR DAUM: Why don't you, and then we will get an answer for both questions from the sponsor.

DR. MANLEY: I echo that concern, and had a couple of questions which, I guess, this could help us.

How can the manufacturer, or is it the FDA assure the committee that we know what the physicians are doing, and saying to patients, and what kind of information patients are getting before they agree, because since it is not an active surveillance system, how can we be assured, with some degree of comfort, that patients know what some of the side effects, or some of the things that are being reported about the vaccine, before they get it?

And that is really tied to the other question about

how can we assure that we have better more active surveillance now that the vaccine has been approved.

CHAIR DAUM: We will ask for a bicameral response. We will hear from the sponsor, and then I think we should hear form the FDA about this, also.

DR. WHEADON: First of all let me say that we, as a manufacturer of pharmaceutical products and vaccines, take any report of an adverse event on any of our products, seriously.

And certainly the things that we heard today we take seriously. That is notwithstanding we have to also understand that the way the post-marketing reports surveillance system works in this country, not just for LYMErix, but for all vaccines, for all drugs, you do not in how these things are collected capture the emotion that we heard here today.

I'm not saying that that is belittling, or minimizing what we heard. But the way the system is you take the sort of emotion and the gestalt, and the stories that we heard, and you have to then transfer that into event terms like arthritis, like arthrosis, like congenital deformities in the case of whatever.

It all goes into a data base where you do your analysis as objective, and as scientific, and in as rigorous a fashion as possible, to discern whether or not there is, indeed, a signal.

And that is something that you've heard Dr. Ball

talking about, that is something you heard Dr. Hoet talk about, and that is something that we do on a daily basis.

So the fact that what we present on the screen did not carry the same weight, emotionally, as what you heard today, I can't give you a better explanation than what I've just given you.

But I can assure that any and every report that we are made aware of is captured and included in the analysis that we presented to you today.

CHAIR DAUM: Does anyone from the agency want to comment on these two questions? Dr. Ellenberg, Dr. Ball?

DR. KEITEL: Yes, I just want to make a specific comment. One of the difficulties we have with VAERS is we often get incomplete information. So one of the specific reasons we are doing a follow up survey focused on reports of joint problems, is to get complete information, both from patients and from their medical records, in the hope of capturing more of the information about exactly the course of the adverse events that are being reported.

DR. MANLEY: My question really related to before the adverse events. I am still concerned about what level of information is transmitted to patients, and how can we be assured that they are getting the information they need prior to the immunization?

And can anyone answer that question?

DR. MIDTHUN: THere are a number of different

things that we can do. I mean, we obviously start with having the package insert or the label. And I think we've heard a lot of discussion today about things in the label that could likely be better addressed.

And we have communicated with the sponsor, and asked them to address certain issues that have arisen since licensure, and as they indicated, they are working on that, and we are awaiting their response shortly, because obviously this is a very important issue.

I think that the label, itself, is primarily designed for physicians. There is a section in the precaution that says patient information. But it is more information that the physician is given to relay to the patient.

And I think that one of the things that we can consider are other avenues such as patient package inserts, or med guides, or other sorts of things to get information directly to the patient.

And I think that, you know, we invite comment on that in the discussion.

CHAIR DAUM: Over and above the package insert maybe Dr. Snider might comment, the CDC and the American Academy of Pediatrics have developed little lay language information sheets for vaccines. I have no idea, does such a thing exist for the lyme vaccine, and is it routinely deployed and available?

DR. SNIDER: There is a vaccine information sheet

prepared for most of the childhood vaccines. I'm not aware of a vaccine information sheet that is used for lyme. Is there one?

DR. MIDTHUN: I think there is one.

DR. MIDTHUN: I didn't see one in our package.

DR. ELKINS: At the time of licensure we were asked to comment on a CDC draft of one, and did so, and it was my understanding that it was proceeding through the vaccine program office. But I confess I'm not quite sure of its ultimate fate.

CHAIR DAUM: Well, I think the committee is going to suggest that the word go out that we think that should be prepared quickly, and deployed fairly aggressively to people who are about to be immunized.

DR. FERRIERI: I must say that in my experience it is uncommon for physicians to read package inserts of drugs, or vaccines, and they are depending on what their nurses may say and read.

But I would never rely on a patient hearing from a physician who has read the package insert, and all the details. You can get all this information off websites, and it is voluminous data, and at submicroscopic level of reading it isn't easy to get through all of it.

You have to be very, very motivated to do that, in my opinion.

DR. MANLEY: I agree, and that is the basis of my comment. That this is intended for the physician and not the

patient. And if a patient has to sign that they have read the material prior to receiving the vaccine, you have a completely different situation in your hands.

CHAIR DAUM: At least in part. Dr. Diaz, you have been patient.

DR. DIAZ: Well, likewise I would just second that a vaccine information statement could be very useful in a setting like this, for patients.

I had two comments. One was something that Dr. Goldberg brought up that actually I was -- when I commented on this, the plan case control study that I was wondering, also, I know there are many states that are developing vaccine registries, and I think Maine is one in particular, and I don't know about the rest of the East Coast, and at what level they have done so, nor whether adult vaccination is really entered into that.

But I bring that up as a potential if such exists that one might be able to, very quickly, identify larger numbers of individuals who have been vaccinated, and perhaps add them, or work with them in a differently, perhaps, study.

The one comment that I wanted to make that I guess is really disconcerting to me, in a sense, is that we don't really have any background population base data, that I'm aware of, regarding some of the findings that are being reported by individuals in association with this vaccine, and how they occur in populations regardless of vaccination, ie, rheumatoid

arthritis, or transverse myelitis.

I recognize the difficulty with some of these diagnosis, and arthritis, as an example, putting all arthritis together, is -- which may be multi-factorial, could be a problem.

And yet it is still very disconcerting to me that the only thing, the closest I think I came to seeing anything suggestive of knowledge of the general population was when someone made the comment we would expect to see more women than men reporting rheumatoid arthritis, and that was the closest we came.

I don't know if the data exists, or how poor the data perhaps is. But, additionally, not having that information, and not having that information age stratified makes trying to sort this out really difficult.

DR. BALL: We have tried to look at background incidents for the arthritic conditions. And, as you are suggesting, there is not much data, only really for rheumatoid arthritis is there some population base data, and even that is fairly limited.

And as you've also just alluded to, we have the additional problem of not knowing the age and gender distribution of vaccine recipients, which both of those factors influenced the incidence of rheumatoid arthritis.

And then there is a number of other limitations in trying to apply that to sort of observe versus expected analysis of the reports that we receive.

DR. DIAZ: And I agree, and I kind of expected that answer, and I guess when we talk about things that might be done, it seems so many times we are sitting here, or other places, with the same kinds of questions, you know, how much of this is occurring in the general population, vaccinated our unvaccinated.

And if there was any way to quickly try and identify that information in some form or manner, again, I realize it won't be pure, but that might be very helpful in the long run.

CHAIR DAUM: Thank you, Dr. Diaz. I would like to -- did you want to make one last comment?

DR. O'FALLEN: Well, pertaining to this issue we certainly have the age and sex distribution of the over 10,000 subjects who participated in the pivotal study.

And I asked exactly this question this morning, what was the expected numbers, and obviously they didn't know. And clearly the rates for rheumatoid arthritis are available for several different kinds of populations, and that could easily have been assessed.

And pertaining to the disconnect, a number of the people that we heard from today said they participated in that clinical trial, and the adverse effects that they reported were never allowed to be reported in that clinical trial.

We had a very small subset of those people in which adverse events were systematically sought out. That has been very disturbing to me throughout the entire discussion.

CHAIR DAUM: Thank you very much. I want to take Dr. Estes question, and then I'm going to pose some scenarios for the committee, and ask for some comment from each member. Dr. Estes.

DR. ESTES: Well, I think this is a vaccine that is used in some very specific areas, and we've heard comments today from people who feel they've had an adverse event from taking the vaccine.

What we haven't heard, and maybe this is not something that is normally done. But there must be data on practices, or specific physicians who use this vaccine.

And this question came up because I recognized a physician in the audience who recognized some complications with a previous vaccine. And that physician, themselves, actually brought this forward and it turned out to be a real event.

Are there physician comments, are there physicians that are very happy in routinely giving this vaccine, and they just don't see a complication with it? Are some of these complications when we have a new physician in a new area, perhaps a patient that goes to the physician and for the first time asks them to give the vaccine.

Are some of these events occurring in those isolated areas where there might be another reason of why there is a problem?

CHAIR DAUM: Well, I'm a pediatrician living in a

pretty lyme-free area. So maybe I will ask Dr. Datwyler to comment on this.

DR. DATTWYLER: Well, one of the things that strike me, and I will answer indirectly, is that what we are talking about we didn't see it in the 10,000 initial study. A big problem.

But if something is fairly uncommon it would slip through. And the highest incidence of this disease is from Rhode Island to Maryland. And that is not what is being looked at.

And I think that there are many physicians in those regions that have probably given a lot of vaccine, and that is probably where the bulk, that is where the bulk of the disease is, that is where the bulk of the patients who receive the vaccine is.

Why don't we encourage a large active study to get to these -- get enough power to answer the question that really needs to be answered, is there a problem, is there a low event but a bad thing happening out there that we have to know about.

And none of the data, to this point, tells us that. And I totally agree with you that there are, probably, physicians who have vaccinated hundreds of people in these endemic areas, and shouldn't they be the ones that are the targets of a very active study, and you can figure out, in their practices, if you can match them with the vaccinated population, and get on with the study and do it.

CHAIR DAUM: Thank you, Dr. Datwyler.

DR. SNIDER: Dr. Daum, could I clarify the issue about the vaccine information sheet?

CHAIR DAUM: Certainly.

DR. SNIDER: We went out and checked on it. For people who are not familiar, there are vaccine information sheets that are required to be developed in relationship to the vaccine compensation program. And so those vaccine information sheets are official, and are really required that physicians use them.

But there is a vaccine information sheet that has been developed for LYMErix. And even though it is not an official one, there is one available. And perhaps it needs to be more widely used.

I don't have any information about how widely promoted and used it is, but one does exist.

CHAIR DAUM: You may hear, in the comments, as we go around, that people would like it put out pretty aggressively by CDC, and made known that it exists, because it sounds like people didn't necessarily know that it does.

I would like to try to move to another phase of our discussion now, and see if we can do that. And that is to deal with the FDA's discussion issue. And to refresh everybody's memory is to please discuss the safety data and the plans for continued safety evaluation of the lyme disease vaccine.

And I would like to make a couple of focusing comments before we call on members to make their own comments.

And that is that we had, as Dr. Ferrieri articulated beautifully, a safety profile view of this vaccine several years ago at the time our opinion was being sought prior to licensure.

And I think the question, as I understand it, that the FDA would like us to think about, has your view of that view changed? In other words, is the safety profile we are hearing about today, in aggregate, both from the manufacturer, and from the FDA, and from the reports from people who journeyed here to talk to us, has something changed? And if so, what kind of response should be made toward that change?

In there you heard considerable detail about programs that have been put into effect by FDA, by the sponsor, to continue to gather safety data. In your view, are those adequate? Are there enough things in place to capture the information you believe we need?

Dr. Midthun asks us to also extend this to the package insert, irrespective of your views of who reads it. Do we need to revise it, is it adequate, is it disclosing sufficiently?

WE've heard comments that could be reiterated as we go around the table. There is, obviously, a lot of basic science missing. I don't think it is the sponsor's sole prerogative to provide that basic science, but this committee is well situated to make a statement that we need it.

What do we need? Let's hear it.

And finally, I've heard a couple of calls for active surveillance of vaccine side effects. That is quite an undertaking. And if you really mean it, when it gets to be your turn give us a sense of how would you do that, and how would you gather data like that, who would pay for it, and how would the data be analyzed and collated.

Other things that people wish to sort of raise and reflect on as we go around are welcomed as well. And to be, variety is the spice of life, so we are going to start today with Dr. Estes and go around to our membership this way. Thank you very much. Dr. Estes.

DR. ESTES: Well, I was not at the Committee meeting when the vaccine was originally licensed, but I think I'm struck by several things.

First I think that Lyme Disease is an important disease. I think it's a disease where a safe vaccine could be very important to our population.

I think that this may be a safe vaccine, but I think my bottom line when I look at everything, and I look at what the recommendations were by the Committee made two years ago, my assessment is that we haven't come too much further past beyond those in terms of answering the questions that the Committee wanted to have answered two years ago.

I personally have some questions about how some of the studies were stratified relative to previous self-reporting

versus Western Blot data.

That's not an area where I'm an expert but I would like expert people to really look at that carefully from some of the original studies.

I found that the studies on the cellular immunity not to be convincing and I think additional studies need to be done.

The studies that were done in the mice did not address, for me, any issues relative to whether this vaccine does or does not exacerbate infection with lyme disease.

I think the pregnancy registry was a start but it's certainly not complete and I didn't come to any conclusions with regards to that. I think the VAERS data is very important but we certainly heard all of the limitations of that data.

I think the follow-up studies there are extremely important and need to be done. I'm concerned about the Phase IV Study. I think everybody's heard really the specific concerns about what -- where we get the data.

I don't think it's coming fast enough and I think other studies really need to be designed to look at the safety of the vaccine.

CHAIR DAUM: Thank you very much. We're off to a good start. That was very well articulated. Ms. Fisher, please.

MS FISHER: Well, as the consumer member of the Committee, I want to thank the members of the public for coming

here and telling what happened to them and to someone they loved after being vaccinated.

I know how hard it is to do that in this kind of forum and if I had been in the audience I would have applauded too to give you moral support.

Last night as I was reviewing the information we were given on Lyme Disease and Lyme vaccine, it became more apparent as I kept going through it, that it was a different disease, different vaccine, same story.

The reluctance, or the willingness of industry and doctors to write off adverse events following vaccination as coincidental, is widespread, and it absolutely impacts on the vaccine adverse event reporting to -- to VAERS.

At the National Vaccine Information Center after 19 years of receiving vaccine adverse event reports, the number one high risk factor that we have identified, is doctor's continuing to vaccinate in the face of clear adverse event symptoms.

And some children are literally vaccinated until they die or are brain damaged because doctors are unwilling to recognize that an event is -- is connected to the vaccine.

The second high risk category is vaccinated with the coinciding viral or bacterial infection. And the third is vaccinated individuals who have a strong family history of autoimmune disease, particularly Rheumatoid Arthritis, thyroid disease and other kinds of autoimmune disorders.

And I found it very interesting that there has been an identification, a potential identification, of a genetic factor, with regard to this vaccine.

I support better labelling by the manufacturer what is known now regarding reported adverse events and also the moving of some of these from a precaution to a contraindication, particularly with regard to vaccinating individuals who had -- have had previous Lyme Disease or have had symptoms of Arthritis, etc. after vaccination.

And, certainly basic science research, FDA-driven basic science research, particularly into antigenetic predisposition to adverse response to vaccination and then, of course, active surveillance of the vaccine adverse events that are being reported around the country.

CHAIR DAUM: Is your view that the basics, that the safety profile of the vaccine has changed, though, since we heard it two years ago, or is this an ongoing concern of yours about the same?

I need a sense of -- that what you're feeling is about the change.

MS. FISHER: Well, since I was not on this Committee when the decision was made all I can say is that looking at what little I know about what the Committee looked at then, this appears to be a continuing problem that -- that is simply magnified now over -- over time, and that it cannot be

dismissed.

We cannot continue to dismiss these as coincidental events, when we continue to have the patterns, and they are clear patterns, and I found -- the reason I made the statement I did is that I found that this -- this is the same with regard to other patterns that have been seen after vaccination.

And, of course, a really good lesson that we learned was with DPT Vaccine. Those patterns were found to be correct because now we are seeing far fewer reactions to DTAP than we did to DPT.

And so that experience, that anecdotal evidence that was presented, has been shown to be correct with the lessening of the symptoms after DTAP.

CHAIR DAUM: Okay. Thank you for clarifying. Dr. Diaz.

DR. DIAZ: Dr. Estes covered at lot of the comments that I was going to make actually.

I, likewise, was not here initially and yet, based on the materials that have been provided to me, and the information set forth, based on the studies and analyses done so far to date in my mind the safety profile of this vaccine hasn't changed significantly in terms of the data from when it was presented for licensure.

That having been said, perhaps that's -- I also tend to agree that there's not enough data, though, to say that it

won't change in -- like this Phase IV Studies that are currently being done I don't feel that, based on the enrollment, that there is enough data there to -- to really make a statement along those lines from the standpoint of -- of the safety.

So I'm actually sitting in a position where I -- almost doesn't matter whether I was here two years ago or here today, I feel like the information is fairly comparable, in a sense.

And, yet, some of the extra data that's been presented -- like the mouse model data, I didn't think was really -- answered any of the questions about autoimmunity in particular.

And I'm not sure that projected studies will necessarily answer all of the questions that have been raised, likewise.

I would be very much in support of further educating the public, certainly, and physicians regarding information about the vaccine; who should be vaccinated and who should be considered for vaccination.

Likewise, I would encourage the FDA to work very hard with the sponsor to address some of the concerns, perhaps such as HLA typing, prior vaccination, etc. and work out some way to -- to at least inform people of those concerns, albeit them not proven at this point in time.

And finally, I again raise my concerns over the

enrollment issues with the studies and it's disconcerting that we -- certainly not from any lack of effort, obviously, on the sponsor's part to do so. It's just that the numbers aren't there and yet the numbers do probably exist out there somewhere.

And I would herald what was commented upon that there probably are many, many physicians who have given hundreds of doses of this vaccine.

And if a study were designed, one could perhaps answer the question a little bit faster than what is currently projected. Albeit, again, I guess I have to say that I don't know how many more people will actually come into the database once the Minnesota and the other groups are enrolled. So I would temper that by looking at those projections.

CHAIR DAUM: Thank you. Before I call on Dr. Manley, I guess just to clarify one thing.

I don't think people needed to be physically present here to compare the database that was available at licensure with where we are today.

Some of the same data were presented this morning and the information has been available. So I would like to hear people's comments as to whether they think it's basically a question of whether there's new concerns or whether they think that we're still -- we have concerns and we still have concerns but -- and we'd like them answered more quickly.

It's a slightly different spin on the same issue.

DR. DIAZ: Right. I might clarify, because obviously, you interpreted what I said, perhaps in a different light. My comment in saying that I wasn't here before and yet, am here today, was not to put forth any concerns about being able to look at the data from that time to now.

It was the issue that there's not very much new data.

CHAIR DAUM: Thank you. Doctor Manley, please.

DR. MANLEY: Well, I essentially concur with what the two previous speakers have said that the concerns that were expressed two years ago seem to be the same concerns that we have today.

And, even though the sponsor said we know a lot more, we have not really resolved some of the issues that were before this Committee then.

I, too, am concerned about the slow enrollment and it seems that at the rate we're going, it's going to take us a long time to answer the questions that, are frankly, quite troubling, I think certainly to me, and I'm sure to others.

And there are some things that are more troubling than others, certainly the pregnancy registry and almost the lack of almost no information in that area that we can really relate to right now.

Certainly pediatric age group and the question that came up near the end of this discussion and that is what patients

know and when do they know it, and how much assurance we have that physicians are communicating with patients about quotes even if they are not proven, some of the adverse reactions that have been reported.

It seems to me that that is very troubling and that whatever we direct FDA and the sponsor to do, going forward, that that has to be addressed and that the surveillance should be much more active than it is currently being described to us.

And that short of being able to address these issues, one has to really look at the cost benefit ratio again.

You know, it's been said many times and outlined very clearly. This is geographic, age distribution, treatable with antibiotic and I think that ultimately this question has to be addressed again by this Commission.

CHAIR DAUM: Thank you, Dr. Manley. Dr. Midthun did you want to make a comment?

DR. MIDTHUN: Yes I would. I think as people go around and perhaps some obviously -- there's been the issue of a higher, the linkage shall we say an association between DR4 and the treatment-resistant Lyme Arthritis and, therefore, concerns whether perhaps a certain HLA type might put you at increased risk for something for vaccine -- for vaccination adverse events related to vaccination.

I guess I would like to just go back though to the efficacy study and visit the issue that likely roughly 30 percent

of the individuals enrolled in that study were DR4 positive just based on what we know of the prevalence of that.

And that we, in that particular study, did not see a difference in the rates of Arthritis or Arthrosis or other things. So perhaps if people might as they go around if they want to address that particular issue and how that might be explored further, given that backdrop, that would be very helpful.

CHAIR DAUM: Thank you and we'll go to Dr. Griffin.

DR. GRIFFIN: Okay. I also was not here two years ago, but I have looked at the data and it seems like that we have more data but what we have is more of the same data. And that what we don't have is any new insights or more in depth examination of the kinds of questions that were raised at that time.

As I think I've already indicated, I don't think the animal model is, contributes much, but it sounds like some other people have animal models, that might actually be useful in trying to sort out some of these issues.

And I think that really needs to be some basic, more basic science approach to a better understanding of the immune response to this vaccine of the types of immunologic abnormalities or whatever may be ongoing, and people who have complications.

And I'm sure that a lot of that kind of information is available for Lyme Arthritis but also for various complications

of Lyme Disease.

But that the opportunities are available for really doing some excellent work and we get hints, I guess is most frustrating to me, is there would be hints that actually studies have been done, the data didn't show much, but we weren't allowed to see that data so there was no way that I can independently say I don't -- you know -- I think that that shows that, you know, it's very reassuring or whatever.

So, I was frustrated by that lack of sharing with us, I guess, the data that does exist, particularly for cellular immune responses to OspA, the relationship of that to HLA, and types.

And I think that would be the kind of data I'd be asking for, would be a better understanding if those people do respond differently than the people that have a different HLA type.

They may not be important but we can probably figure that out. But those kinds of studies ought to be done and they ought to be shared.

I certainly agree with the need to get active, some sort of surveillance that answers the question that basically, I think, Dr. Luft said most directly: Is there a problem or isn't there?

And, right now, I don't think any of us feel comfortable in saying there's not a problem or uncomfortable in

saying there definitely is a problem. We just really don't have the data on which to be able to make that judgment.

So those are the things that I would suggest.

CHAIR DAUM: Thank you very much Dr. Griffin. Let's move on to Dr. Kim, please.

DR. KIM: Well, I also agree that we still have similar safety concerns remaining with us compared to two years ago. Again I did not perceive any improved understanding or knowledge on those issues whether I feel more safer now than two years ago.

I think is the same concerns are currently under investigation and ongoing. But I think it requires continued investigations to address the issues that have been with us for the last two years.

And the second issue, again, along the lines, again everybody, the previous speakers have indicated issues regarding HLA DR and OspA interactions.

I think that certainly needs to be addressed soon in a format that is scientifically of acceptable fashion and at the same token we have seen many vaccines have changed the format over the years.

So if, indeed, you know again, we all agree that this is important this is, therefore, vaccine is needed, then I consider the current vaccine as, perhaps, first generation.

Then I think that we need to look into, a perhaps,

second-generation vaccine which, if that is possible, then perhaps, eliminating the cross-reacting epitopes, apparently that -- those regions do not overlap with the protective epitopes.

I'm sure that those kinds of constructs can be serum proteins and purified proteins can be constructed and I don't know whether they would be functional or not, but if indeed they are then I think some of the issues then need to be considered for developing safer vaccines for Lyme Disease.

And then, third issue, is I also support that some sort of a vaccine package needs to be developed to indicate or to at least to share the concerns that have been presented to us today with the consumers and physicians.

I think they need to know what is going on, you know, whether this is real or not, you know, there was a meeting to address these issues. I think they need to know that.

And then, lastly, there is a study going on in pediatric population I'm very concerned about that despite, you know, having all the issues discussed today and I soon like to see a very close monitoring of a pediatric studies for the safety and other issues that have been brought to our attention today.

CHAIR DAUM: Okay. Thank you very much, Dr. Kim. Dr. Stephens, you're up.

DR. STEPHENS: I think the comparative safety data that's been presented really hasn't changed, in my opinion, from what we saw from the '98 review.

I wasn't on the Committee at that time, but certainly, the data provided doesn't suggest that there's been a significant change. What has changed in my mind is the weight of what is largely anecdotal data, but certainly a huge body of anecdotal data suggesting that there may be, that we may be missing something with this vaccine.

I think that's the concern of -- of many of the Committee members. I'm bothered by the issue of this vaccine in the setting of prior Lyme Disease and I'm also bothered by the issue of this vaccine with certain HLA types.

And I don't think we know a lot about the immune response to Borrelia in general or specifically to this vaccine.

I would certainly, a point made about active surveillance in endemic areas is something that I think should be strongly considered as well as increased patient information and potential increasing warnings regarding the package, package insert.

CHAIR DAUM: Thank you very kindly, Dr. Stephens. Dr. Snider.

DR. SNIDER: Well I was here. I remember, and I think there is one thing that's different about the atmosphere and that is that the characterization of Lyme Disease was different at that meeting, and that there were a number of people from the general public who made comments about how devastating Lyme Disease had been.

And I do recall very vividly subsequently when the Advisory Committee on Immunization Practices released its statement about Lyme Disease should be considered for people in certain high risk areas with certain high risk activities, that in that we made some comment, which seems rather benign, to the affect that most cases are treatable with antibiotics, that we received thousands of letters from the public indicating that that wasn't true.

And, that there were a lot of treatment failures and we weren't being as supportive of the vaccine as we should.

And so I just remind people of that particular environment, and that information that people delivered.

With regard to the concerns, I guess since some of my quotations were in the written document it's clear that I had concerns at that time about long-term affects.

I think we do have some more data, and I appreciate the sponsors obtaining that additional data for us. Unfortunately, as in many cases with many vaccines, when we're talking about uncommon events, if not rare events, we don't have enough data to be able to draw any definitive conclusions.

And so I would agree with a lot of my colleagues here that the concerns that we had back then have not been completely alleviated, and in fact, additional studies that had been done in the interim have raised our concern.

And we certainly are concerned about what has

happened to the people who spoke here, and their family members, and have a great deal of concern about whether that is related to the vaccine or not.

As Dr. Estes pointed out, you know, a number of studies could be done from the standpoint of animal studies, in vitro immunologic studies, clinical studies, and so forth.

But I think we have to choose very carefully because there aren't unlimited resources.

I do think the post-marketing cohort study was an excellent idea as I think everybody else is very disappointed, and I'm sure the sponsors disappointed as well, with regard to the enrollment of persons into that study and the fact that we don't have more information now.

I do have concerns when we talk about doing active surveillance, although on the surface it sounds like it might be -- help pick up more cases, it would have to be done in a way that doesn't bias the study as Dr. Platt alluded to.

Because if everybody knows that you're looking for certain conditions that might result from LYMErix, then that's what they'll give you.

And, therefore, you would have to do a very carefully designed study in a manner that I haven't thought of exactly right now. That's not to say it's impossible, but to more aggressively go after cases and invoke vaccinees and controls.

The registry idea is something that I wouldn't

totally give up on. I think it's worth exploring. I realize that all of these things would be quite costly and logistically difficult and may not get us down the road any more rapidly than what -- the speed we're going with regard to the post-marketing cohort study that's already been designed.

I am very concerned about the potential long-term effects, and one of the things we haven't talked about is, you know, how long will efficacy remain in future years, are there going to have be additional boosters?

And if there have to be additional boosters will that present additional problems. So I think the problems with this vaccine are going to continue to be in front of us, or at least the potential problems.

I agree with folks who indicated that there need to be some modifications in the package insert and that we should more aggressively promote a vaccine information sheet that has the appropriate information.

I apologize I didn't look at the package insert but it sounded to me from what Sid Wolfe said that in the indications area perhaps need to be modified to reflect the geographic risk as well as the activities risk.

I think the manufacturer already has indicated a desire to put in something about hypersensitivity reactions.

And then there is the issue of what to say about the possibility of chronic arthritides or other autoimmune

diseases. And I don't think we have definitive information that indicates that those are long-term adverse events.

On the other hand we do have some plausible hypotheses that have not been disproven and so it's not clear to me in this kind of a setting how one deals with that in a vaccine information sheet or in a package insert in a way that is understood by the average practitioner or the average patient.

CHAIR DAUM: Thank you very much Dixie. I'm going to do a little bit a reverse field here because there are some -- we're starting to encroach on airplane schedules, assuming that planes are running on time.

And, we'll actually start at this end of the table with Dr. Ferrieri and work our way up, if that's okay. And, we are aiming for a 5:30 adjournment. So, please be succinct, if some things already been said in some detail, you can merely say that you agree with it.

But please feel free to expand on points, should you wish to. Dr. Ferrieri

DR. FERRIERI: Well, I was here the last time on this subject, also. Dear BBC, New York Times, London Times and CNN and everyone else, please don't call my office.

I don't return any calls on Lyme vaccine. What I say is part of the public record. It will be posted on FDA's website. Sorry if that seems intractable but I feel that we can only be misquoted on what we say.

I had my chance to say several things at the beginning today, so I won't reiterate them. I feel that there is more data to examine, but the concerns that I had personally before have not been assuaged by anything I've heard today. And I feel the background noise that we're hearing may be greater.

My concern is greater than it was before and there are several areas that we have not yet been able to gain information on that I commented on before and that Dr. Snider has resurrected, the issue of further boosters, the length of protection, etc.

In a nutshell, I think FDA has to grapple with the serious issue of is it sufficient to do revisions to the package insert. Well, that really -- how far will you be pushed to have to do something more drastic than that, Dr. Zoon and Dr. Midthun, et al?

I think that you have to deal with what you have in front of you. Are we going to be able to resolve these issues expeditiously or should you put a moratorium on the vaccine until you are able to very critically examine what we have and what is realistic to move forward.

It's with great regret that I say this to you. I've never had to say this before. I've never heard, in all of the years I've been on the Committee heard this type of concern iterated without Agency response that has satisfied the dissatisfying from my point of view.

I consider what we're dealing with today to be very, very serious and I would like to throw back to you the need for you all to reexamine how this fits in to your mission and in the public health realm.

And, so, I agree with others who would like more basic science work done as I iterated in the beginning. The Phase IV Study dissatisfaction may not, perhaps it will come forward sooner -- maybe not.

There are too many ifs here for us to feel secure that the answers will be forthcoming.

So, again with great regret, I think that you have to examine where you are and what we owe to the public.

CHAIR DAUM: Thank you, Dr. Ferrieri. Dr. Myers, please.

DR. MYERS: Well, I think we do have more data. I wasn't here. And, it's reassuring, but it's very limited. It's a cross-over design functionally.

I think it's important to say that at this point there is no evidence of chronic arthritides being associated with the vaccine.

That said, though, I think everybody's expressing the same concern that such an association could exist, it has biologic plausibility. I've heard a couple of people comment that they suspect that the possibility of a VAERS signal, and that this needs to be aggressively pursued.

I think the concern that I have is that we need the data as quickly as we can possibly get it from as many sources as possible to allow the assessment of likelihood of causation versus coincidence.

I just don't think we have that. I think vaccine information, providing vaccine information, is -- it would be very important.

But I think the real issue that I would like is to see an aggressive approach to getting the data to allow an assessment. I think the Cohort Study is really important. It's going slowly. It's going to be an important study and I think it's important not to dilute it or allow it to collect data that isn't accessible across the whole study

With that said, there are an enormous number of vaccinees that aren't being collected that are in areas where the attack rate for Lyme Disease is much higher than Massachusetts.

Rhode Island, I guess, is going to be part of the Cohort Study. But, there's Connecticut. There's Long Island. There's all the way down through the mid-Atlantic States.

And I think it's really critical that we try and get that data as quickly as possible so that we can do the assessment that needs to be done and either say that this is a problem or we can allay the concerns about it. I guess that's it.

CHAIR DAUM: Thank you very much, Marty. Dr. Goldberg.

DR. GOLDBERG: I was not here two years ago, and I must admit, as I reviewed the materials, that I might have had difficulty approving the vaccine at the time -- voting for approval at the time.

I don't see sufficient new data. And it makes me very nervous that the rate of accrual of new data is too slow. And so, what I would urge, is that with all speed, you start to do some surveillance. Whether it's active surveillance, registries in combination with the ongoing efforts.

Because I think you have to cover the bases on a lot more fronts than you are and much more aggressively if you want to get some resolution.

I do believe that patient information has to be made much more accessible. One possibility is that that all done, that all provided, the rates of vaccination will decrease even more and so it will become even harder to definitively collect more data.

And I think you have to weigh all of these, somebody has to be, the FDA and the sponsor have to be working out what the numbers are and what kinds of timetables you have to come up with to get some of these projects underway.

I also was concerned about the discussion of case definition that came up in the open part of the hearing. And, the fact that in the original studies this very specific definition was used and I would urge, that if it's possible, to reanalyze

that data with sliding definitions of cases. And determine, what kind of affects misclassification on case definition could have on the efficacy results.

I don't know if that was done. There wasn't enough detail provided. Basically, I think everything else I would say was covered already.

CHAIR DAUM: Thank you very much. Are there any more airplane concerns on the remaining people that need to speak or can we just go in sequence? Good. Dr. O'Fallen.

DR. O'FALLEN: I too was underawed by the amount of data that were available two years ago regarding adverse affects, and read with a great deal of interest about the Cohort Study that we now hear is in serious jeopardy.

But that was why I was asking so much about it because I thought it would be so essential. I think those data collected in a systematic a way as possible, and I truly do approve of the design of the study that is currently underway and I only wish that they could access more data. I think we do need more data.

There is evidence that something's going on out there, I truly believe, and my answer to the question that was posed so eloquently and so frequently from the floor several times today, is no.

CHAIR DAUM: What question is that?

DR. O'FALLEN: Would I take the vaccine.

CHAIR DAUM: Dr. Davis, please.

DR. DAVIS: Thank you. I have several issues that I certainly concur with our prior speakers regarding. Not in any one particular order.

One question I have would be the impact on what we haven't heard and unfortunately we didn't hear in a more of an anecdotal way, from one physician, who had provided a letter for us to read.

But what is the impact on the occurrence of Lyme Disease in communities where the vaccine has been more widely used? Are there any decent surveillance data in those communities where we can get at least some assessment of trends in actual occurrence of the disease?

Some of these communities may be actually smaller and I think being able to make an appropriate assessment of data in those communities may be difficult to do. But I think very important.

Along those lines, what Dr. Dattwyler had recommended earlier, doing an objective assessment of physicians experienced with using the vaccine and their experience with side effects, I think would be important.

I certainly concur with that and I'd also want to make sure that the whole issue of their recognition of side effects is important as well, because of the issue that was raised, are people not adequately recognizing what may actually be

an event.

So I think probing that, of course, would be important to do.

One thing I'd be interested in also, is knowing how often in the occurrence of Lyme Disease, OspA is actually encountered. Certainly as a construct for the vaccine.

I think this is a very unique vaccine and I think a lot of thought went into the design and I think it was very clever. But what is the rate of human encounter with OspA and when.

We certainly heard about the issue of it being -- well at least some immune response to it being produced later in the course of illness. But I'd certainly want to know more information about that.

The whole issue of basic research on OspA I think is very important given what we now are learning more about regarding the whole issue of autoimmunity. And then the issue of enrollment in the Phase IV Study.

One question I would have would be: What can be done to enhance the enrollment without compromising the quality of data? Do you have to go to smaller HMO's that have smaller databases but nonetheless have high quality data? Would that be the type of data that would be needed?

You have to balance that with the HMO's that may have the appropriate quality data may have been asked to participate in a lot of other studies because of the very nature

of the quality of their data. So, clearly, there is a dichotomy here but perhaps one that should be explored a bit further.

And then the other issue I think that I had some questions about is the whole issue of reactivation. Some of the Western Blot patterns certainly presented in a bit anecdotal way in the information that we had to read are very interesting and I'd want to know more about that.

CHAIR DAUM: Thank you. Dr. Coyle?

DR. COYLE: Well, I was here two years ago, and the safety profile has changed, and it has changed for one real reason. Although the information presented on the 8,000 or so that have had the vaccine suggests this seem to be safe in the majority of individuals.

There is now, which wasn't a few years ago, the suggestion that in a minority of individuals, a few of those this vaccine can produce a devastating, a generalized chronic pain syndrome that really disrupts lives. And there was not a hint of that at all.

And the only data for that are the testimonies that I've heard. Because it's not captured anywhere else. So I think that's of concern. That wasn't raised two years ago in my opinion and that indicates that there's a subset of individuals in whom it's a bad thing to get the vaccine. That it can be potentially a very devastating thing.

I think that the Cohort Study -- the reality is it

sounds that they're not going to get 25,000 patients in a reasonable time frame. So something has to be done, something has to be done to increase the numbers because it just doesn't sound like they are going to get it.

Secondly, I think we need to learn more about the sorts of patient testimonials that we heard or heard about from letter. We know very -- we know nothing about these patients.

So let's get a registry of these patients to try to figure out what seems to be the background to try to cull out a group that may be at risk where you don't want to give this vaccine.

Finally, the preliminary, very sketchy, I mean 30 pregnant patients, and we have data on a minority of them and the data that we have available is very bothersome. I think we need to get some real pregnancy data. That should be a real push. That's disturbing.

And finally, I think something does need to be added to the patient insert -- to the package insert here. Even if we don't have clear cut data, the fact that it's now been raised that in, granted perhaps a very small minority, but in a small minority, this can be a bad thing to take, potentially.

It needs to be put in somehow that this has been raised as a question and investigations are ongoing, etcetera, so that people can know about it; and physicians.

DR. LUFT: I'll just make a couple of comments

because I've commented enough today. If you look at the sponsor's data, there's no difference. I think that that's what they've stated and they showed us the data. There's no significant difference.

What's the problem? The problem is -- it's a problem of perception and a problem of confidence. And I think that that's a really big problem.

I think that everybody in this room whose involved with vaccine design or administration realize that that's a very large problem. It's a problem of perhaps why this vaccine has such poor uptake within the community.

And it goes on both sides now. My feeling is I was here two years ago. There were certain suggestions that were made. My expectation is that the company, that the sponsor, would have been very vigorous in doing it. Actually they got a gift.

They were approved for a vaccine for this disease which was really very unique in many ways. It's mode of action was unique. It was the first lipoprotein that was licensed, that was given an indication.

It was a new -- it was all new -- and you would have expected -- and it was done in record time if I remember. It was really done in a very short time.

And I'm disappointed today. Because I hear some information here and I hear some information there. And I don't hear good data. We really are sitting in a situation in a sea of

just what we feel. Because no one is giving us data.

And the same thing could be said on the science part of it. Two years ago the group described the issue of the whole LFA. DR4 was something that was there. It's now being talked about as if it's gospel.

There was nothing that came out, or very little that I know of that's come out since that time. There hasn't been anybody that has really come out and validated that work. That has looked at this patient population, etcetera, etcetera.

My greatest fear is that this is a big disease. When we talked about, I think Dixie was talking about that his perception was that there were a lot of people that were suffering. And I can attest to the fact that in our community, that Lyme disease was and is a very big issue.

It's not that there is no need for a vaccine. What I think there is a need for is a vaccine that people have confidence in. There's a need for a vaccine that, once it's given its license or indication that there will be ongoing research and surveillance, that will meet the privilege of being out there and the public being administered to -- to patients. I just don't think that's being done.

So I know there have been a number of suggestions that have been made as to how we can more vigorously and actively get to the answer as to whether adverse events are actually occurring or not actually occurring.

And I support that wholeheartedly. I support much smarter people than me making those suggestions on how those types of studies should be done.

But at the end of a short time we should be able to come back here and get real information and not feel that we're on a ship that's sort of in the middle of a storm.

DR. RAY: I want to I want to comment briefly from an epidemiologic perspective. First, I think there is a real basis for safety concern with this vaccine. Back of the napkin calculations suggest that 5 to 6% of current VAERS reports are reports for this vaccine which seems large given that its uptake is less than expected.

So I think there is a basis for safety concerns.

Second, I don't think that the post-marketing studies that are planned are going to achieve their power objectives. And for that reason, I think studies with greater precision are needed be they Cohort studies or a variety of methods or case

control studies.

DR. DATTWYLER: Well, I was here two years ago and as a matter of fact I was sitting in this seat and I also had the last word at that time.

CHAIR DAUM: I have the last word.

DR. DATTWYLER: Oh you have the last word. I meant of the panel. You know I totally agree with what most of the

people have said. I think that Dr. Snider's point of the atmosphere at that meeting versus the atmosphere in this meeting is very important to realize.

And ultimately physicians have to decide what's best for their patients. And to do that in an intelligent way you need to know the risks and the benefits.

And as I sit here, like everybody else, have no greater feeling for what are the risks of this vaccine than I did two years ago. And that's bad. And I totally agree with what Dr. Myers said and what Dr. Loft said and everybody else is that we need to get that data so we can plug that into a risk-benefit analysis and make an intelligent choice for our patients.

Vaccines and drugs, we know can have adverse reactions. If you know what the adverse reactions are and the incidence of those adverse reactions and then you know what the risk that your patient runs, then you can make an intelligent choice and right now we can't make an intelligent choice. So I agree that we need to, like everybody else, that we need more data.

CHAIR DAUM: Dr. Ellenberg.

DR. ELLENBERG: Yes, I'm sorry. I just want to make a quick clarification on the back of the envelope calculation. I think we have somewhat over 1,000 reports, is that right, on Lyme Disease vaccine. We have well over 100,000 total reports in the database. We've been getting 10 to 12,000 reports

a year. So it would be more like under one percent I think of the total.

DR. RAY: Well let's think it through though. You get about 10,000 a year, according to the documentation. And there have been 1,100 reports approximately in two years so that is 550 over 10,000.

DR. ELLENBERG: Okay. That's not what I --

DR. RAY: I would come up with about 5 percent of current reports or 5 to 6 percent are for this vaccine which seems to me high.

CHAIR DAUM: Well just to sort of anchor and to try and not be repetitive. I, of course, was here two years ago also and am grateful to Dixie and others for making the comment about how different the atmosphere was then.

But I still don't feel that it's appropriate to apologize for that decision. I actually think it was a correct decision to go forward.

I'd like to, before I say anything, remind everybody that this meeting we had today was very unusual in that the FDA has called us together to talk about a licensed product -- to get our sense of where we think the safety data are. And I think that's a tribute to the agency's concern.

I'm also profoundly moved by the patients and families who took the time to come here and talk to us. But I had some concerns about the safety profile two years ago and some

concerns about the efficacy two years ago and I believe I'm on the record as having articulated those.

I'm not sure whether I believe that there is convincing evidence of new safety concerns or not. And that may be a statement of where things are and perhaps should not be. I can't accept the notion that this study can't be done anywhere else.

The case control study is going forward so slowly because there are no other quality sites to do it and I am very disappointed that that hasn't gone forward more quickly.

I applaud Dr. Ball and colleagues for taking VAERS reports which are very difficult to make head or tail out of, separate numerator data from denominator data and trying to nest a case control study within that to look at some important issues as well.

I'm disappointed that we're not further ahead I guess in understanding the safety issues of two years ago and remain unsure of whether we've deteriorated or behind or not. I didn't hear convincing evidence that there are major new concerns despite all the comments that were heard.

The package insert does need to be updated. At the very least reflect issues like hypersensitivity that have come to light since two years ago, but they appear to be relatively minor in the overall scheme of things.

I think the people who came to talk to us today

from all over the country -- that their comments need to not go unheeded. And what I would suggest is to begin to see if what Dr. Lufts said is true. Are those reports not in any of the databases? Are they not in the manufacturers pre-licensure database? Are they not in the VAERS database?

I would like to really find out whether that's so. Because if your conclusion is correct that they're really not, then something is wrong with our system. Something is really wrong with our system. And, once I've made that determination, I would then go forward designing studies to address some of the diverse complaints that the patients and their families had, which by themselves, need some thought as to how frequently they're occurring.

The information sheets takes a lesson out of the pediatric vaccine book and patients who take this vaccine or any vaccine have got to be informed of what they're getting into.

And so, I highly applaud that and believe that Dr. Manley's comments are difficult to implement because we can't standardize what patients are told in this country but nevertheless, having the sheet available like that, would go a long way to providing the framework for a physician or a provider to have dialogue with a patient.

So I think that we've really had a wonderful meeting here. We've heard lots of points of view. I think the call for Dr. Ferrieri and others that more basic science needs to

be done to address the issues that are unknown about the pathophysiology of this disease are beyond the scope of dealing with just the vaccine -- but also intimately tied up with it. They can't be neglected. But I'm not sure we can solve those problems in this room.

I want to thank everybody who took the time to share views with us and debate these issues with us. I think we've had a wonderfully informative day. Before we stop, Dr. Ellenberg will have the last word.

DR. ELLENBERG: Well, I just want to say that that certainly some, perhaps many, or even most of the stories that we've heard today, have been reported to VAERS and they are included in the summaries that Dr. Ball presented and I would certainly urge that anybody here who has not made those reports, do, because that's the only way we know what is happening if those are reported.

As Dr. Ball described, he is going to be following up on these reports to try to and have a better understanding and a grasp on all of these types of reports that we have received.

CHAIR DAUM: Thank you for clarifying that and this meeting is adjourned.

(Whereupon, at 5:25 p.m. the above-entitled matter was concluded.)