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 lipoprotein 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

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.

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

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