FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

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MEETING

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THURSDAY,
MAY 18, 2006

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The meeting convened at 9:00 a.m. in Salons A, B, and C of the Hilton Washington D.C. North/Gainthersbury, 620 Perry Parkway, Gaithersburg, Maryland, Monica M. Farley M.D., Acting Chair, presiding.

ADVISORY COMMITTEE MEMBERS PRESENT:

MONICA M. FARLEY, M.D.	Acting Chair
SCOTT EMERSON, M.D., Ph.D.	Temporary Voting Member
BRUCE GELLIN, M.D., M.P.H.	Temporary Voting Member
MICHAEL GREENE, M.D.	Temporary Voting Member
SUSAN KRIVACIC	Temporary Voting Member
PHILIP S. LaRUSSA M.D.	Member
SAMUEL MALDONADO, M.D.M.P.H.	Acting Industry Rep
LAURI MARKOWITZ, M.D.	Non-Voting Member
PAMELA McINNES, D.D.S.	Temporary Voting Member
KENNETH NOLLER, M.D.	Temporary Voting Member
CINDY PROVINCE, R.N. M.S.N.	Consumer Representative
WALTER ROYAL, III, M.D.	Member
ELIZABETH UNGER, M.D.,Ph.D.	Temporary Voting Member
MELINDA WHARTON, M.D., MPH	Temporary Voting Member
BONNIE WORD, M.D.	Member

FDA STAFF PRESENT:

CHRISTINE WALSH, R.N.	Executive Secretary
NANCY MILLER, M.D.	Medical Officer, Office of Vaccine Research and Review, Division of Vaccines and Related Products Applications
KAREN GOLDENTHAL, M.D.	
HENRY HSU, Ph.D. M.P.H.	
HECTOR IZURIETA, M.D.	
JOSEPH TOERNER, M.D. M.P.H.	

SPONSOR PRESENTERS:

ELIAV BARR, M.D.	Senior Director, Vaccines/Biologics Clinical Research, Merck & Co., Inc.
PATRICK BRILL-EDWARDS, M.D.	Director, Worldwide Vaccines Regulatory Affairs, Merck & Co.
JANINE BRYAN	
ADRIAN DANA	
LAURA KOUTSKY, Ph.D.	University Washington
MYRON LEVIN, M.D.	University of Colorado
LISA LUPINACCI	

PUBLIC HEARING SPEAKERS:

AMY ALLINA	National Women's Health Network
DEBORAH ARRINDELL	American Society Health Association
BOBBIE S. GOSTOUT, M.D.	Society of Gynecologic Oncologists
KATHRYN GUCCIONE	Women in Government
SUSAN E. HOLLERAN	Coalition of Labor Union Women
BETH JORDAN, M.D.	Medical Director, Association of Reproductive Health Professionals
KRISTEN MOORE	Reproductive Health Technologies Project
MARTHA NOLAN	Society for Women's Health Research
ELLEN STOVALL	National Coalition for Cancer Survivorship
SEAN TIPTON	American Society for Reproductive Medicine

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

9:00 a.m.

DR. FARLEY: I'd like welcome everyone to this VRBPAC meeting this morning and thank you all for your attention. I'm going to immediately turn over the introduction to Christine Walsh, who will make a statement.

MS. WALSH: Good morning. I'm Christine Walsh, the Executive Secretary for today's meeting of the Vaccines and Related Biological Products Advisory Committee. I would like to welcome all of you to this meeting of the Advisory Committee.

Today's session will consist of presentations that are open to the public. I would like to request that everyone please check your cell phones and pagers to make sure they are in the off or silent position.

I would now like to read into the public record, the conflict of interest statement for today's meeting.

The Food and Drug Administration is convening today's meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of

1972. With the exception of the industry representative, all members and consultants of the Committee are special Government employees or regular Federal employees from other agencies and are subject to the Federal conflict of interest laws and regulations. The following information on the status of this Advisory Committee's compliance with Federal ethics and conflict of interest laws, including, but not limited to 18 U.S.C. 208 and 21 U.S.C. 355(n)(4), is being provided to participants in today's meeting and to the public.

FDA has determined that members of this Advisory Committee and consultants of the Committee are in compliance with Federal ethics and conflict of interest laws, including, but not limited to, 18 U.S.C. 208 and 21 U.S.C. 355(n)(4).

Under 18 U.S.C. 208, applicable to all Government agencies and 21 U.S.C. 355(n)(4), applicable to certain FDA committees, Congress has authorized FDA to grant waivers to special Government employees who have financial conflicts, when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest, Section 208, and where

participation is necessary to afford essential expertise, Section 355.

Members and consultants of the Committee who are special Government employees at today's meeting, including special Government employees appointed as temporary voting members have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their employers, spouse or minor child related to discussion and recommendation, on the safety and efficacy of a human papillomavirus vaccine, Gardasil, sponsored by Merck and Company.

These interests may include investments, consulting, expert witness testimony, grants, contracts, teaching, speaking, writing, patents and royalties and primary employment.

Today's agenda involves a discussion and recommendation of the safety and efficacy of a human papillomavirus vaccine, Gardasil. In accordance with 18 U.S.C. Section 208(b)3, no waivers were required for today's discussion. Dr. Ruth Karron, Dr. John Modlin and Dr. Steven Self have recused themselves for today's discussion. Dr. Samuel Maldonado is serving as the Acting Industry Representative, acting on

behalf of all related industry and is employed by Wyeth Research. Industry Representatives are not special Government employees and do not vote. This Conflict of Interest statement will be available for review at the registration table.

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

FDA encourages all other participants to advise the Committee of any financial relationships that you may have with the sponsor, its product, and if known, its direct competitors.

Thank you. Dr. Farley, I turn the meeting over to you.

DR. FARLEY: Thank you, Christine. Well, once again, welcome everyone to this discussion today about the safety and efficacy of the human papilloma recombinant vaccine. I want to, once again, welcome the panel and I'd like us all to go around the table and introduce ourselves. I'll start by introducing

myself. I'm Dr. Monica Farley. I'm from Emory University in Atlanta and I'm serving today as the Chair of this session.

Why don't we start with Dr. Royal at the end of the table.

DR. ROYAL: Walter Royal, the University of Maryland, School of Medicine.

DR. NOLLER: Ken Noller, Tufts University School of Medicine and Tufts New England Medical Center, Boston.

DR. GREENE: Michael Greene, Harvard Medical School and Massachusetts General Hospital and I'd just like to take one second to point out that there's a little error on the roster. I do not have an MPH. I only have an MD. I don't know how that MPH got there. Thank you.

MS. WALSH: We do apologize for that, Dr. Greene.

DR. MALDONADO: Sam Maldonado, Wyeth Research, Industry Representative.

DR. MCINNES: Pamela McInnes, National Institutes of Health.

MS. PROVINCE: Cindy Province, St. Louis Center for Bioethics and Culture. I'm the Consumer

Representative.

DR. GELLIN: Bruce Gellin, National Vaccine Program Office, Department of Health and Human Services.

DR. EMERSON: Scott Emerson, University of Washington. I'm a bio statistician.

MS. KRIVACIC: Susan Krivacic, Patient Representative, Austin, Texas.

MS. WORD: Bonnie Word, Baylor College of Medicine, Texas Children's Hospital.

DR. UNGER: Elizabeth Unger, Centers for Disease Control and Prevention.

DR. MARKOWITZ: Lauri Markowitz, Centers for Disease Control and Prevention.

DR. WHARTON: Melinda Wharton, Centers for Disease Control and Prevention.

DR. LARUSSA: Philip LaRussa, Columbia University, College of Physicians and Surgeons.

DR. FARLEY: Thank you. I would like to start by pointing out that we have a fairly busy schedule today, a fairly packed agenda. We do have many people who have signed up to participate in the open public hearing this afternoon, so we will try our best have ample discussion, but to keep it moving so

that we can come to a final vote on the questions that you've been provided in your packet today. And we'll start out the program with the FDA representative, Nancy Miller, who will give us an introduction to today's activities.

DR. MILLER: Good morning and welcome to the VRBPAC meeting to review the Gardasil DLA. We're just going to start with the questions for the Committee and then we'll go into the presentations as scheduled.

The first question for the Committee is do the data from studies 005, 007, 013 and 015 support the efficacy of Gardasil for the prevention of HPV 16, 18, related cervical cancer, cervical adenocarcinoma in situ, cervical intraepithelial neoplasia grades two or three or worse in females 16 to 26 years of age?

The second question, do the data from studies 007, 013 and 015 support the efficacy of Gardasil for the prevention of HPV 6, 11, 16 and 18, related VIN, Vulvar Intraepithelial Neoplasia, grade 2/3, and Vaginal Intraepithelial Neoplasia, grade 2/3, in females 16 to 26 years of age?

Do the data from studies 007, 013 and 015 support the efficacy of Gardasil for the prevention of

HPV 6, 11, 16 and/or 18, related condyloma acuminata or warts, Vulvar Intraepithelial Neoplasia one and Vaginal Intraepithelial Neoplasia grade one?

Fourth question, do the immunogenicity data support bridging of the younger female population nine to 15 years of age to the efficacy population, females 16 to 26 years of age?

Five, do the safety data from studies 007, 013, 015, 016 and 018 support the safety of Gardasil for use in females nine to 26 years of age?

And the last, please comment on post-marketing commitments.

DR. FARLEY: Thank you, Dr. Miller. Well, at this point then, we will proceed with the sponsor's presentation and I think there are two speakers, Dr. Barr and Dr. Brill-Edwards.

DR. BRILL-EDWARDS: Good morning and thanks for attending. We're here today to share results of clinical trials using Gardasil, which is Merck's quadrivalent human papillomavirus vaccine. This vaccine is currently receiving a priority review because of its potential to meet an un-met medical need.

Now, in the health sciences, there is

nothing more rewarding than being able to contribute to meeting an un-met medical need. I'd like to draw your attention to a comment Sir Isaac Newton made to a colleague who was complimenting him on his contributions to science, and that's that, if I have seen further, it's by standing on the shoulders of giants.

Now, in our case, we are standing on the shoulders of the basic scientists whose observations about this virus led to the concept to the vaccine and to the many clinicians and scientists who developed and implemented the successful cervical cancer screening programs that we have today.

We're excited about these results because Gardasil has the potential to build on the success of cervical cancer screening programs and provide clinicians with the first vaccine to prevent cervical cancer. After this brief overview, Dr. Eliav Barr will present a detailed discussion of our results

In general, Gardasil is a vaccine indicated for the prevention of cancer, pre-cancerous or dysplastic lesions, genital warts and infection caused by the HPV types targeted by the vaccine.

Cervical cancer is caused by HPV. HPV

infection is common. Life-time risk for infection is 50 percent. In the U.S. the life-time risk for developing Cervical Intraepithelial Neoplasia or CIN, is 25 percent and over 10 percent of adults will develop genital warts due to HPV.

Cervical cancer is the second most common cancer in women worldwide. There will be approximately a half a million new cases and 290,000 deaths each year. Despite Pap screening, American women remain at risk. There will be approximately 10,000 new cases each year, 3,700 deaths, or put another way, 10 American women will die each day from cervical cancer.

There is currently no approved vaccine for the prevention of cervical cancer. Therefore, an Advisory Committee, very similar to today's procedure, was convened in 2001 to consider the clinical endpoints that would serve as the basis for licensure.

At that time, Merck proposed that studying cancer itself isn't feasible, because it takes too long and it disadvantages too many women. We also had to consider that most HPV infections in pre-cancers regress. So, there was the need to consider an endpoint that had a direct link to cancer. And

pointing to the success of cervical cancer screening programs, their success is due to the detection and definitive therapy for CIN 2/3, and that's what we recommended as the basis of licensure and ultimately, that's what the Advisory Committee recommended.

To profile the vaccine, as I mentioned, it's a quadrivalent. It contains four HPV types. Two types, 16 and 18, are so-called high-risk because they're responsible for 70 percent of cervical cancers. The other two types, six and 11, though not commonly associated with cancer, are responsible for 90 percent of genital warts.

The virus-like particles that we use are manufactured in yeast, which is a well-established vaccine manufacturing method and it's absorbed to Merck's aluminum-hydroxy-phosphate-sulfate, which has a well-established safety record. The vaccine is intended to be used in a three dose regimen at zero, two and six months. It's not a live-virus vaccine and therefore, the VLP's cannot cause infection or disease.

To review a brief overview of what a VLP looks like, on the left side of the slide, you'll see the L1 proteins that are produced and then they self-

assemble into pentamers, also known as capsomeres, and a typical VLP represents 72 to of these capsomeres in a hollow sphere. It's this hollow sphere that the immune system sees.

To preview Dr. Barr's presentation, we've studied Gardasil in over 27,000 subjects in 33 countries. Gardasil, like all vaccines, is most effective when given before exposure to infection. In that prophylactic setting, Gardasil is efficacious and it's this high efficacy that forms the basis of the priority review. The vaccine is immunogenic, it induces an immune response that's many-fold higher than natural infection and it has an excellent safety profile.

Specifically, Gardasil is indicated for the prevention of the following, due to types 16 and 18, cervical cancer, cervical adenocarcinoma in situ, CIN 2/3, vulvar and vaginal cancer, VIN grades 2 and 3, VaIN grades 2 and 3, but also, it's indicated for the following, due to all vaccine types, CIN 1, genital warts, VIN 1, VaIN 1 and HPV infection.

To remind you, cervical cancer is caused by the human papillomavirus. Gardasil prevents disease caused by the most common HPV types and

Gardasil has the potential to meet an un-met medical need as the first vaccine to prevent cervical cancer.

Merck has several consultants in attendance today and I'd just like to acknowledge them. We have Dr. Laura Koutsky, Professor of Epidemiology from the University of Washington. We have Dr. Michael Cunningham who is the head of the Cranial Facial Medicine Program, also at the University of Washington. We have Dr. Mark Stoler, a Professor of Pathology from the University of Virginia. Dr. Myron Levin, Professor of Pediatrics from the University of Colorado and Dr. Janet Wittes, who is the President of Statistics Collaborative.

And now, I'd like to ask my friend and colleague, Dr. Eliav Barr to give you a detailed discussion of our results.

DR. BARR: Good morning. My name is Eliav Barr. I'm head of the clinical program for Gardasil, Merck's quadrivalent HPV vaccine. I really wanted to thank the Committee for the opportunity to present the results of our clinical program.

Merck's HPV vaccines have been in clinical trials for over nine years. The program has enrolled over 27,000 women and children in 12 separate clinical

studies. To summarize this comprehensive clinical program, I'd like to spend a few minutes reviewing the clinical significance of the disease, talk a little about how we designed the clinical program to address efficacy, immunogenicity and safety, provide an overview of the keys findings with regards to efficacy, immunogenicity and safety, and then describe all of this data into the overall very favorable benefit risk profile for Gardasil.

Now, HPV is a potent carcinogen. It tends to infect the squamocolumnar junctions of the genital tract, the anal mucosa and the aero-digestive track. On infection, the virus causes disordered cellular proliferation, which can result in malignant degeneration.

HPV infection is necessary for the development of cervical cancer. All cervical cancers arise from HPV infected tissue. HPV is also an important contributor to cancers of the genital tract in both women and men and is an important contributor to certain head and neck cancers.

Now, HPV also causes benign tumors, including low-grade cervical vulvar and vaginal dysplasia that are the most common reasons why women

have Pap test abnormalities, genital warts and recurrent respiratory papillomatosis, which are rare diseases, but very devastating, warty tumors of the larynx.

Now, these lesions are not malignant, but they cause enormous amounts of morbidity and a lot of health care costs.

HPV is the most common sexually transmitted infection world wide. Over 50 percent of Americans will become infected with HPV at some point in their life times. In women, this infection is manifested by the third of cases in CIN, grade 1, cervical intraepithelial neoplasia, grade 1 or low-grade dysplasia. So, the life time risk of this lesion in American women is one in six.

A smaller proportion of women will develop CIN 2/3 or AIS, that's cervical intraepithelial neoplasia, grade 2/3, moderate to high-grade, cervical pre-cancer or adenocarcinoma in situ.

In the absence of cervical cancer screening, the life time risk of cervical cancer is about one in 30. Pap testing and other means of screening have reduced the risk of cervical cancer in countries where screening is available from -- by

about 75 percent, so that's decreased the risk from about one in 30, to about one in 120.

As I mentioned, HPV also causes genital warts and about one in eight, men and women, in the U.S. will develop a case of genital warts at some point in their lives.

Cervical cancer is the most important disease caused by HPV infection. Around the world it's the second most common cause of cancer in women. Eight-hundred women will die every day from cervical cancer world wide. Cervical cancer mortality and morbidity. The impact on society is accentuated by young age of its victims.

There are two kinds of cervical cancer, both of which are completely HPV related. Eighty percent is squamous cell variant, and that's proceeded by CIN lesions, and about 20 percent are adenocarcinomas and those are proceeded by adenocarcinoma in situ. It's worth noting that adenocarcinoma rates have been increasing in the United States over the past years because Pap testing doesn't detect this kind of cancer very well and HPV infection rates have been increasing in the population.

Now, Pap testing and HPV testing, more recently, has been in a very important public health program and has reduced the rate of cervical cancers by 75 percent in the U.S. But there is significant costs associated with this approach. HPV infection is very frequent, so women have to be screened frequently, and that translates to approximately 50 million Pap tests every year that yield about three and a half million Pap test abnormalities every year in the U.S., which require some form of follow-up and that leads to the diagnosis of 1.4 million cases of CIN 1 or low-grade dysplasia and 330,000 cases of CIN 2/3, all of which require substantial amount of follow-up and treatment.

In addition to the morbidity that it causes to women, these lesions -- and screening programs are very expensive. They cost over four billion dollars a year in the U.S. every year.

Now, despite the availability of screening, around 10,000 American women will develop cervical cancer. The reasons for this is either non-compliance with screening, lack of regular availability for health care, or the inherent limitations of the sensitivity of the Pap test. And

this 10,000 rate means about 10 American women will die of cervical cancer every day.

HPV also causes vulvar and vaginal cancer at around 40 or 50 percent. That translates to around 3,500 cases a year. These lesions are very similar in natural history to cervical cancer and it's also worth noting that the instance of vulvar cancer in the U.S. has increased in women less than 50, again, due to the increased incidents of HPV infection that then results in vulvar dysplasia and cancer.

Now, HPV infection also causes cancer in men and the sources of those cancers are shown here. About 10,000 American men will develop an HPV related cancer every year in the U.S., mostly in the head and neck, anal canal and the penis.

As I mentioned, HPV causes genital warts. The life time risk exceeds 10 percent in both men and women. That means in the U.S., about a million new cases a year in American men and women.

Now, these lesions are not malignant, but they are very painful and they are very psychologically damaging, particularly to young people who tend to get them.

Treatment is also unsatisfactory. The

visible genital warts is really the tip of the iceberg of a much broader field infection that therefore, requires significant rounds of therapy with ablation. It's very difficult to get rid of them. Typically you need three rounds of therapy and even then, 30 percent of these lesions recur. So, this is pretty substantial public health problem.

And finally, HPV also causes recurrent respiratory papillomatosis. This is a really devastating disease, due to infection of the vocal folds in the larynx with HPV types. It causes hoarseness and airway obstruction and that airway obstruction requires quite a bit of surgery.

There are two types of binormal-distribution of RRP, a juvenile variant and an adult variant. The juvenile variant occurs in boys and girls age three to four, roughly. It's a very, very aggressive disease that requires on average, four separate surgeries every year to clear the airway obstruction and make sure that the person can breathe, and malignant transformation can spread to the lung and other organs in the airway and is not uncommon. Adult RRP is also quite a significant public health problem. Typically, it occurs in people in their 20's

and 30's.

So, I think I've shown you that HPV infection causes significant amount of morbidity and mortality in the U.S. Every year over four million Americans are impacted by a new diagnosis of an HPV related disease.

HPV is a highly endemic infection and prophylactic vaccination is an excellent way to prevent highly endemic infectious diseases and on the basis of that, Merck decided to develop a prophylactic HPV vaccine.

And the technology that we decided to use was based on the observation that when the L1 capsa protein, the outer coat protein of the virus, is expressed in recombinant systems, it self-assembles into a virus-like particle that looks just -- very similar to the wild-type virus, without of course, the infectious properties. And in animal models of papillomavirus infections using these L1 VLP's, we were able to show that vaccination resulted in protection from infection disease, but neutralizing antibodies were induced, and most importantly that when you transfer serum from vaccinated animals to unvaccinated animals, you also transfer protection.

And that just demonstrated the critical importance of humeral immunity and circulating antibodies in the way in which this vaccine mediates its efficacy.

So, on the basis of these promising preliminary observations, we developed a very stable technique to manufacture highly purified L1 VLP's using recombinant yeast technology. This technology has been used in a variety of vaccines that have been given in hundreds of millions of doses to infants, children, adults around the world over the past 20 years.

So, the vaccine that we chose to develop is Gardasil. Gardasil covers the HPV types that are responsible for the majority of clinical HPV disease in the U.S. The four type are HPV 16 and 18, and six and 11. These two are the cancer causing HPV types, that are responsible for 70 percent of the all of the HPV related cancers in both men and women and they're also responsible for the majority of the high-grade pre-cancerous lesions. Also, they are responsible for 25 percent of low-grade dysplastic lesions. These are the very common lesions that are the major finding when women have a Pap test abnormality.

Now, HPV 16 and 18 infection in men, not

only causes cancer in men, but it also the primary means of transmission of this malignant HPV type to women.

HPV six and 11 together cause about 90 percent of genital warts in women and men, as well as 90 percent of RRP lesions. Of note, they also cause 10 percent of the CIN 1 lesions and these are clinically indistinguishable from the CIN 1 lesions that are caused by the high-risk types. So, here women are told that they have a pre-cancerous lesion, when in fact, no such risk exists.

And then again, HPV six and 11 infection in men, not only impacts men, but it's, men are the primary vector for transmission of HPV to women and again, infection in men is the cause of the acquisition of disease in women.

So, a vaccine that targets these four HPV types would target a large burden of HPV infection and a successful vaccine would really reduce the burden of HPV disease in the U.S.

And so, once we chose to evaluate this particular vaccine, we set about to design a clinical program that would address the key issues in terms of the prophylactic efficacy of this product. And I

wanted to share a little bit about that with you on the rational of the clinical program and why we chose the particular studies that we did.

Now, at the inception of the phase three program, Merck and FDA met and agreed that the primary basis for licensure was to -- was based on the demonstration of the prophylactic efficacy of Gardasil, to show that Gardasil is efficacious in preventing HPV 16 and 18 and related cervical cancer. That would be the primary basis for licensure. We also discussed a variety of different end points.

We also understood that the studies would continue and that separate from licensure, we would do supplemental analysis at the end of the phase three program, not only to look at the impact of the vaccine on type-specific disease, but also to get a clearer picture of the impact of Gardasil on the overall burden of clinical HPV disease, regardless of the causal HPV type. And those analysis will be available next year.

In 2001, the VRBPAC Committee of -- at the time, met to discuss the basis for licensure of prophylactic HPV vaccines. And it was obvious to everybody that the key benefit that such vaccines

might provide is prevention of cervical cancer. But it was also obvious to the Committee that that end point wouldn't work in a clinical trial setting. First of all, although HPV infection is necessary for the development of cervical cancer, there is a long time delay between infection and the development of cancer.

But more importantly, it was clear that those studies -- that any studies that would be done would require very intensive Pap testing and the best possible screening opportunities for women who participate in this study. And so, most of the cervical cancers would then be detected at the CIN 2/3 or AIS stage and would be excised as per standard practice, and so, we would never be able to reach the cervical cancer end point.

So, the Committee looked at earlier end points and the first one that they considered was HPV infection. After all, it's a necessary pre-requisite to cervical cancer. But most HPV infections clear and so, it wasn't clear whether or not we would prevent the types of infection that would lead to cancer.

They looked at CIN 1 and in deed, these

lesions also tend to clear. They are also not on the critical path to cervical cancer.

So, attention focused on CIN 2/3 or AIS. These are the targets of cervical cancer screening, and we know that the way in which Pap testing works in HPV testing, is that it allows physicians to detect CIN 2/3 or AIS and to excise those lesions before they progress to cervical cancer. And in countries where this is the only lesion that's treated, the rates of reduction in cervical cancer, mediated by cervical cancer screening, is the same as in countries where more aggressive approaches are used.

So, it was clear that this is the way in which Pap testing works. And so, if a vaccine could prevent these lesions from occurring from the outset, we would be able to demonstrate the efficacy of the vaccine with respect to cervical cancer, and that's what is the primary objective of the program, to demonstrate that the vaccine prevents the development of HPV 16 and 18 related CIN 2/3 and AIS caused by new infections.

The rational for the vulvar and vaginal cancer end point really followed the same approach that we used for the cervical cancer end points, and

this is because HPV related vulvar and vaginal cancer have a very similar natural history studies. They all arise from HPV infected highly dysplastic tissue. And in case series of un-treated VIN or treated VaIN 2/3, the rates of progression to cancer were actually quite substantial, 16 percent of every interval of 3.9 years and two percent over two years. So, these are excellent surrogate markers for vulvar and vaginal cancers related to HPV.

We had also key immunogenicity and safety objectives. The most important one was to bridge the efficacy findings in 16 to 26 years olds, to nine to 15 year old pre-adolescents.

Now, Gardasil is a prophylactic vaccine. It will be most effective when it's administered to populations prior to entry into the risk period, and that's the age group 15 and below.

Now, we also knew that it was not feasible to do efficacy studies in this population because of limitations on discussions of sexuality and of HPV sampling in very young pre-adolescents. So, FDA and Merck agreed that we could bridge the efficacy findings in 16 to 26 year old to the younger age range using immuno-bridging approaches.

Immunogencity was also used for -- to evaluate the duration of efficacy and immune response to Gardasil, as well as to examine how the vaccine interacts with other common adolescent vaccines.

A critical parameter of our clinical program was safety and we sought to comprehensively define the safety program of Gardasil and all of the populations for which the vaccine would be indicated.

We also knew that this vaccine would be given to women of child-bearing potential, so right from the beginning, we set up a program that would really evaluate in great detail, all the pregnancy outcomes that would occur and subject to receive Gardasil, regardless of the temporal association between the time that they received the vaccine and the time that they became pregnant. So, throughout the course of the clinical trials.

Now, I have alluded to the various age ranges of the clinical program, and I wanted to explain why we chose this particular age range, and the way that I wanted to explain it is by showing you when HPV infection hits the population. And the way that I'm showing you this is by the incidents of new genital warts in the large private insurer data base

in the U.S. And I choose genital warts as a marker for HPV infection because they happen very quickly after infection starts and also, it's very detectable. People know when they have genital warts and they can immediately report it. So, it's a really good marker of the temporality of the infection relative to age.

And what you can see is, you can see the age by different buckets here and the new case rates, males and females, and in the early teens, there's very little genital warts, very little HPV infection. But starting with the time of sexual debut, there's just an enormous increase in the risk of these diseases and the peek age is in 16 to 26 year olds, and that's where we chose to do our main efficacy studies, 16 to 26 year old women.

And for the immuno-bridging analysis we evaluated nine to 15 years old, the period just prior to entry into the period of acquisition of HPV infection. And so, what we were looking for is an indication for the vaccine to be used in nine to 26 year old age range.

We also knew that this program would last for several years. We wanted to look at long term duration of efficacy. We also wanted to evaluate the

vaccine in a large population of subjects. And so, we decided to develop a clinical info-structure that would really allow us to combine all studies together and to have consistent ascertainment of safety and efficacy over a long period of time.

So, we trained the investigators to use a standardized approach to collection of specimens. The same approach was used in all clinical trials. Central pathology laboratory was used for all cytology and pathology work. Everything was processed through our central lab. HPV detection was done in one location in one laboratory. We had a validated pathology panel whose sole responsibility was to read slides for the purpose of end point evaluation. And then a large data -- the data sifting monitoring board was used in all the large clinical trials. And so, together we were able to ensure that we had accurate and complete representation of the efficacy end points, as well as safety.

So, now I'd like to talk a little bit about the clinical trial results. I'll start with describing the study population, then talk about efficacy and I'm going to talk about two kinds of efficacy. One is prophylactic efficacy. This the

primary basis for licensure, which is the impact of administration of Gardasil to HPV naive subjects on the incidents of the various diseases that are caused by these four vaccine HPV types.

I'll also share with you preliminary population impact analyses that evaluate the impact of Gardasil in the overall incidents of HPV disease, regardless of causal of HPV types. As I mentioned, these analyses are scheduled for formal evaluation next year at the end of phase three, but we will provide you with some early estimates of efficacy. I'll also show the bridging immunogenicity study, describe the duration of efficacy of the vaccine and describe the safety profile.

Now, the clinical program enrolled over 27,000 subjects around the world in 33 countries and five continents. So, it allowed us to look at a variety of variations in ethnicity, countries of origin, socio-economic circumstances, co-morbidities, so it was very diverse. The ages that we chose were those ages that would benefit most from administration of a prophylactic HPV vaccine, girls and boys age nine to 15 and 16 to 26 year old adolescent young adult women.

A critical feature of the program was that the vaccine enrolled women regardless of baseline HPV status and this was because we knew that this vaccine would be administered without prescreening and so, we wanted to get information in the general population. This was also by the way, a recommendation of the VRBPAC of 2001, who felt very strongly that women who were infected at baseline should be included in the clinical trials to at the very least, evaluate the safety of the vaccine in that population.

And as a consequence of that, there were some women who were infected at day one, who had got disease, but this is not what Gardasil is about. Gardasil is a prophylactic vaccine and in some analysis, these disease was counted in the end points and this was -- we knew that that was going to happen, but it was very important for us to ensure that we had a broad population enrolled in the clinical trials.

The end points that we chose really span the severity of HPV infection from persistent infection to low-grade dysplasia, high-grade dysplasia and up to carcinoma in situ.

We evaluated the full spectrum of cervical, vaginal and vulvar disease in women and we

allowed in the clinical trials, some variation in the management of an abnormal Pap test so that we could represent the diversity and approaches of physicians in the U.S. and outside of the U.S., used for managing women who present with a Pap test abnormality. So, we tried to mimic the entire spectrum of care patterns that would already -- that have already existed.

And so, now I wanted to point out the -- start talking a little bit about prophylactic efficacy and I just want to share a little bit, the way in which we approached the evaluations of prophylactic efficacy.

We did four clinical studies, protocols, five, seven, 13, and 15. Protocol five was an HPV 16 vaccine study. It's an HPV 16 prototype in Gardasil, the same material that was used for the HPV 16 component in Gardasil. The key strength of this study is the fact that it had long term follow-up, The longest term follow-up in the data base.

There is also protocol seven, which is a dose ranging study. And then two pivotal phase III studies, protocol 13 and protocol 15. Protocol 13 was designed to look at the impact of the vaccine on CIN of any grade, as well as external genital lesions,

here we call it EGL's. And so, this protocol included an intensive evaluation and genital inspection, as well as an evaluation of frequent Pap testing.

Protocol 15 was designed to be a real world study to look at the impact of the vaccine on cancer. Women underwent yearly Pap testing as is the typical standard in the U.S. And the triage outcome in this approach was very similar to that used by the ASCCP guidelines, used in the U.S.

Now, we also knew that we would do pre-specified analyses to combines studies together to improve the precision of efficacy estimates. And for end points that involve six, 11, 16 and 18, all four types together, we combined all the studies of Gardasil, so that's these three studies.

And for the most important end point the study, which is HPV 16 and 18 related CIN 2/3 or adenocarcinoma in situ, we combined all four studies together, five, seven, 13 and 15.

This is the baseline characteristics of the population. There are about, in the efficacy population, about 21,000 were enrolled, median age - mean age of 20, great majority of them were sexually active and we've already started to see some evidence

of sexually transmitted infections at baseline, four percent incidence of chlamydia, for example.

Most importantly, we already had a very significant amount of CIN at baseline. Twelve percent of the population had a diagnosis of ASC-US or worse on their Pap test. That's one in eight subjects who already were infected at baseline, already had potential CIN at baseline. These are lesions that Gardasil would not impact, but we included this because we again, wanted to include a population that was broad, had a diverse background, similar to the general population.

Twenty-seven percent of the population was positive to at least one of the four vaccine HPV types. That meant that 73 percent of the population was completely naive to the four HPV types. Among the 27 percent, most of the women were positive to exactly one HPV type. So, in these women, most of these people were naive to the other three and we could look to see whether even though they were infected with one type, whether the vaccine will provide efficacy looking forward in those women.

Now, the principle efficacy end points for the study are presented here. The primary end point

for the program was HPV 16 and 18, related CIN 2/3 and AIS. This is the surrogate for cervical cancer, similar approach to vulvar and vaginal cancer by surrogate. A burden of disease impact -- analysis, looking at all CIN caused by the four types. And then an evaluation of all external genital lesions caused by the four HPV types.

I'm going to talk a lot about end point cases and I just want to explain what an end point case means. Every area of abnormality -- first of all, we trained all the colposcopists in this precise way in which we wanted to biopsy suspect lesions. Every area of abnormality was biopsied and placed in a separate container. They were then sent to the central lab and fixed -- and processed and put into paraffin and then each biopsy was cut into 13 sections. The first two and the last two were put on slides, were then H & E stained and were read by the pathology panel.

The intermediate pieces were sent to the PCR lab where DNA was extracted and typing was performed. A case is defined for our analyses as being positive to one of the four vaccine HPV types and having the path panel diagnosed, one of the

several HPV related diagnoses, and that represented a case.

Now, Gardasil is a prophylactic vaccine. It's designed to prevent infections that lead to highly morbid conditions, but we enrolled subjects regardless of the baseline HPV status.

So, we performed our analyses in women who were naive to the relevant HPV types at baseline and did separate analyses to evaluate the vaccines impact on infection that's already present at baseline. And I wanted to show you how we did our case counting for the primary prophylactic efficacy analyses.

Now, as I mentioned, about 73 percent of the population was naive to all four types and they were eligible for any of the four HPV -- four types of end point, six, 11, 16 and 18. Among the 27 who were infected with at least one type, most were positive to just one type. So, let's take a look at an example. If a women was positive to one type here, let's say HPV 18, and was naive to the three other types, if she developed an end point caused by the other types for which she was naive, she was an end point. But if she developed an end point caused by the type for which she was already infected, she was not considered an

end point for prophylactic efficacy analyses. She was considered an end point for other analyses that we used to look at the overall population impact, as well as the therapeutic possibilities that this vaccine might have.

There were two prophylactic efficacy populations that were pre-specified. The primary analysis was to be in the per-protocol population and this was designed to approximate the impact of Gardasil in adolescents who have received all three doses of the vaccine prior to exposure to vaccine HPV types.

The HPV naive modified intention to treat analysis was the broadest population for prophylactic efficacy and was really designed to evaluate the impact of giving Gardasil to adolescents and adults, giving at least one dose before they become exposed to the particular vaccine HPV types.

To explain the inter-play between these two populations, I wanted to show you what each of these populations included. So, the protocol included about 87 percent of enrolled subjects. HPV naive population, 95 percent of the enrolled subjects participated in this population. So, the per-protocol

population included women who were naive to the relevant type at day one, remained free of infection through the course of vaccination, had follow-up visits, did not violate the protocol, received all three doses of vaccine, and then the end point counting started after the completion of the three dose vaccination regimen.

With respect to the broader HPV naive population, we included any women who was naive to the relevant HPV types at day one and had any follow-up visits. Our case counting started one month post-dose one.

So, the difference between these populations included that the broader population included people who became infected during the course of the vaccination, any protocol violators, anyone who received less than three doses or didn't have any follow-up visits after month seven and anyone who actually developed an end point between month one and month seven, and some women did, in fact, develop such end points.

We had pre-specified the timing of the analyses. These analyses would occur when the requisite number of end points cases would be observed

in the per-protocol population of the relevant studies.

After the primary analyses, we agreed that the studies would continue. We would follow women up for a longer duration of time and we would also wait until the pre-specified triggers for the population based analyses would be met, and this is the analysis of the impact of the vaccine on CIN 2/3 caused by HPV types, regardless of whether they are vaccine or not vaccine related. And the trigger is likely to occur in the early part of next year.

So, now I wanted to provide you the primary results of the program, with respect to specific end points. For each end point I'm going to talk about the definition of the end point and rationale for the end point, the study -- the primary studies in which the end point was evaluated, the statistical criteria for success, the results of those primary analyses and then, pre-specified supplemental analyses that were conducted.

The first one, of course, is the cervical cancer end point. And for proof of cervical cancer prevention for HPV 16 and 18, the primary end point was CIN 2/3 and AIS, as agreed to by the 2001 VRBPAC.

This is the immediate and obligate precursors to cervical cancer caused by the types in the vaccine. We pre-specified that we had to be successful in two sets of studies. The first one was protocol 15, the CIN 2/3 efficacy study, and the second one was a combined analysis of all of the efficacy studies of Gardasil in order to increase the precision of the efficacy observed in protocol 15.

The pre-specified primary analysis was in the per-protocol population. These are the statistical criteria for success. And then there were supplemental analyses in the broader HPV naive population, looking at the primary end point and then focusing on the highest grade lesions that we observed in the program, CIN 3 and AIS.

So, this is the primary result of protocol 15. In the protocol population there were 21 cases of HPV 16 and 18 related, CIN 2/3 or AIS. All were in the placebo group, 100 percent efficacy, highly statistically significant result. You'll notice that there were 16 and eight cases for 16 and 18 related in diseases, and so, we sought efficacy for each of these components. You'll also notice that this number is, when you add them up, 16 plus eight, is larger than

the 21, and that's because three women had both 16 and 18 related CIN 2/3. They are counted once in the composite end point and one in each of these end points.

In the broader HPV naive population, again, protocol violators, people who became infected immediately after vaccination, starting follow-up right after the first dose is given, efficacy remained very high, 97 percent.

Now, when we looked at the combined analysis of the phase II and III clinical trials, there were 53 cases of the primary CIN 2/3 and AIS end point, all were in the placebo group, again, 100 percent efficacy, p-value of highly statistically significant, efficacy for both types and high efficacy again, in the broader HPV naive population, 99 percent efficacy.

We focused also on CIN 3 and AIS. CIN 3 is high-grade dysplasia and includes squamous cell carcinoma in situ. AIS includes adenocarcinoma in situ and what we saw was high efficacy, 100 percent efficacy in this population. This is the closest we could get to a cervical cancer end point and what was particularly interesting is that there is an efficacy

for both the immediate precursor of squamous cell cancer and the immediate precursor of adenocarcinoma. And nine versus zero here, a high efficacy.

We used the same approach to evaluate vulvar and vaginal cancer. These are the immediate precursors to HPV related vulvar and vaginal cancer, VIN 2/3 and VaIN 2/3. We knew that this was uncommon cancer and these lesions were relatively uncommon. And so, we decided that are primary analysis would be in the broadest population possible. The combined analysis data set for Gardasil trials, because protocol five really focused just cervical disease, we did not include this in this population. And anyway, it was an HPV 16 vaccine.

Again, as I mentioned, to try and get as many cases as possible, we pre-specified that we would do this in the HPV naive MITT population. Statistical criteria for success was, this was a pre-specified exploratory evaluation and these are the results. There were 24 cases of HPV 16 and 18 related, VIN 2/3 and VaIN 2/3, all were in the placebo group, 100 percent efficacy. So, this analysis demonstrated the prevention of this particular lesion and the cancers associated with it.

So, just to summarize the key end points in the clinical program, we were able to show that prophylactic administration of Gardasil was highly effective in preventing cervical, vulvar and vaginal cancers caused by the two HPV types in the vaccine using pre-specified surrogate markers. And the impact of this is rather substantial. Just looking at cervical cancer around the world, this vaccine has -- the impact -- has a potential to impact up to 350,000 cases of cervical cancer every year world wide.

I wanted to switch now to talk a little bit about the CIN of any grade in AIS and this analysis was really designed to look at the burden of disease caused by new infections with these vaccine HPV types. And in the U.S. that burden is very substantial. Around 700,000 cases of CIN are diagnosed every year in the U.S. due to these four HPV types. And so, showing a reduction in those types would be quite an important finding.

The primary evaluation was in protocol 13. This study was designed for detection of CIN of any grade. We did supplemental analyses in the combined data set of efficacy trials that evaluated Gardasil. We pre-specified the primary analysis for protocol.

This is the statistical criterion for this particular study with respect to efficacy. And then we did supplemental analyses in the HPV naive population, both of protocol 13, and in the combined efficacy studies to look at the broad population of women who are naive at baseline at day one.

And these are the results of protocol 13. There was 37 cases of the primary end point. All of them were in the placebo group, 100 percent efficacy, highly statistically significant result. We saw cases in efficacy for each one of the four vaccine HPV types and in the broader population, we saw a high efficacy that continued, 97 percent.

In the combined analysis efficacy was 95 percent. Again, we saw efficacy for all of the four HPV types. The four cases in the Gardasil group were all CIN 1 lesions that were detected very early after the end of the vaccination period. They were not break-throughs due to waning immunity. When we look at the broader HPV naive population to efficacies nearly identical to the protocol, 94 percent.

Finally, I wanted to review the external genital lesion prophylactic efficacy. The end point that we chose here was to look at the full spectrum of

diseases caused by the four vaccine HPV types. Again, this is a highly morbid disease that is responsible for 900,000 or so cases a year of genital warts and other lesions. The primary evaluation was in protocol 13, which was the study designed to focus on this end point and then we did supplemental analyses in the combined data set for Gardasil. Again, protocol five was not included because it didn't evaluate genital lesions.

The primary analyses were per-protocol. We had a pre-set statistical criterion for success and then supplemental analyses in the broader HPV naive modified intention to treat population, both of protocol 13 and the combined efficacy analyses.

And these are the results of the primary evaluation of this end point. In protocol 13 there were 40 cases in the placebo group -- 40 cases of the end point, all were in the placebo group, 100 percent efficacy, a highly statistically significant result.

Of note, most of the lesions were actually six and 11 related. This is in keeping with the fact that HPV six and 11 is by far, the predominant cause of genital warts and that's why here, these lesions are more predominant then in the previous end points,

which were more 16 than 18 related. High efficacy continued in the modified intention to treat population of this study.

Looking at the broader population of external genital lesions, efficacy was 99 percent. There were 113 versus one case. This one case again, occurred shortly after the completion of the vaccination regimen, was not due to waning immunity. It was an HPV six related condyloma. And again, efficacy remained high in the HPV naive modified intention to treat population.

Now, we did some other pre-specified analyses that were important to fill out the picture of efficacy. I mentioned before that there were a significant amount of women who were infected with one HPV type, but were free of infection with the other three. And so, we looked to see whether the vaccine remained efficacious for the remaining three, even though they were already infected with one HPV type. And the answer is yes, efficacy remained high, similar to what I showed before, for those women who were infected with one type, looking at efficacy for the other three.

We looked at the various baseline

demographic characteristics, ethnicity, sexual behavior, co-infection, other co-morbidities, concomitant medications. Efficacy was uniform.

And then right from the beginning, we decided that for the per-protocol population, we understood that we wanted to try and make it as real life as -- as real world as possible, with respect to dosing and we knew that adolescents would be -- it would be a hard time to get them to come at a zero, two, six vaccination regiment. So, all we required for entry into the per-protocol population was getting three doses of the vaccine in a one year period. Any kind of dosing regimen of three doses in a year was acceptable for per-protocol.

So, what we've been able to show in the primary results of our study is that prophylactic administration of Gardasil to 16 to 26 year old young women is highly effective in preventing cervical, vulvar and vaginal cancer caused by the two vaccine HPV types using the surrogate markers that I mentioned, reducing the burden of cervical disease caused by the four HPV types and reducing the burden of external genital lesions caused by the four HPV types, including genital warts.

So, with that, I'd like to switch gears and talk a little bit about population impact and this is the -- defined as the impact of the vaccine on rates of CIN and external genital lesions caused by any HPV type, not just the vaccine types. And the particular analysis that we chose -- that we found probably most important is what's called the prophylactic population impact. And the question is a public health question about if Gardasil is given prior to sexual debut, what could we expect to be the magnitude of reduction in the overall risk for cervical cancer in the population?

Now, in a broad population of pre-adolescents, their risk over their lifetime for cervical cancer is due to vaccine or non-vaccine types.

Now, to answer that question, one has two choices. You can either do an efficacy study starting in pre-adolescence, but for reasons of difficulties in dealing with sexuality in young kids, that's not feasible. So, instead, one can model the impact in a population of young women who are completely HPV naive, naive not only to vaccine types, but to a whole host of other genital HPV types and these are 14 HPV

types that cause 95 percent of cervical cancer and if the women are naive to all of these types, they are basically HPV naive and would be a good model for adolescence.

Now, we've done the analysis for the four HPV types and consistent with our approach of doing prophylactic efficacy with the first licensure, supplemental filing dealing with population impact, we're still working through all of the testing for all of these other 10 HPV types and will have the results at the end of phase III. But to provide a preliminary estimate of population impact, we looked at a population based on the results of these. We didn't have these data, so we used something else as a surrogate to make a completely naive population.

So, what we have in our primary evaluation are women who are negative to the four vaccine HPV types. We don't have the results for the other 10 types, so we substituted a negative Pap test at day one for the HPV status for these 10 types.

Now, I have to say, a Pap test is not a good substitute for HPV testing. It's not as sensitive and what happens is, a negative Pap test only excludes 65 percent of CIN 2/3 and AIS present at

day one caused by non-vaccine HPV types. Also, if a women is infected and hasn't yet developed CIN 2/3, the Pap test won't really pick this kind of person up.

So, the result is, that while we were trying to model a population that was adolescent, in other words, completely unexposed to HPV, the best that we can do at this stage is a population that includes women who are predominantly HPV naive, but still have CIN 2/3 and infection at baseline that was not picked up on the Pap test.

Now, this impacts the efficacy of the vaccine, of course, because these lesions are already present at baseline, the vaccine is a prophylactic vaccine and early in the study where most of these end points are occurring, the vaccine would have little efficacy, but then later on, as this population acquired new infection and then disease due to that new infection, the vaccine's efficacy becomes more apparent. So, we had expected that efficacy would be lower than what we will see at the end of phase III.

So, what is the efficacy that we would expect? Well, the efficacy for the overall population is simply the efficacy for the types in the vaccine, multiplied by the proportion of the overall CIN 2/3 to

AIS caused by 16 and 18. At this stage in our clinical trial, 55 percent of the CIN 2/3 lesions were 16 and 18 related. So, our expected efficacy would be at least 55 percent.

But what we saw, as we expected, was that efficacy was a bit lower, 38 percent, slightly higher for the individual components. And this is because we couldn't exclude all of that baseline HPV infection, all the baseline disease caused by non-vaccine types. And to show you what I -- how we approached this, I'll show you a time to event curve.

What you see here is the cumulative incidence of CIN 2/3 over time. We required the women to have a negative Pap test, so the first time they were -- any CIN was detected was at the month six visit. White is placebo, yellow is Gardasil.

In the first parts of the study, of course, there is the vaccine in the placebo, the lines are right on top of each other, and these are CIN 2/3 and presumably HPV infected subjects at day one. Gardasil is not a therapeutic vaccine. It shouldn't impact the course of infections that are already present at day one, nor does it cause regression of CIN 2/3 lesions. So, this is not what Gardasil is

about. It's a prophylactic vaccine.

Looking over the course of time, women develop new infections. Those new infections then cause disease and we can see that the event rates are very different between placebo and Gardasil. The curves separate and continue to separate, so over the course of time we have more and more apparent vaccine efficacy. And we expect at the end of phase III to have a complete estimate of the efficacy of the vaccine, probably close to the 55 percent that we anticipate or maybe even greater.

I want to switch gears now to look at the immunogenicity bridging study, which is a -- it was a very important component of the program. As we mentioned, studies in HPV naive young adolescents are not feasible, for the reasons I stated. And so, Merck and FDA agreed that we would use immuno-bridging to bridge the efficacy findings in 16 to 26 year olds to nine to 15 year olds, by demonstrating that their immune response in the children were non-inferior to those in adults.

We measured that in at month seven, which is one month post-dose three and we looked at the Geometric Mean Titers in the children and compared

them to the adults. We did a ratio of the GMT's in kids versus adults, and of course, if they're not inferior, then the ratio would be at least one. And what we saw was here -- this is Geometric-fold ratio, this is the four HPV types, and so, when you compare boys to women and girls to women, you see that the anti-HPV levels at month seven are substantially higher in all of the children compared to the adults, and particularly high in boys. And so, these results -- so, we met the criterion for immuno-bridging in this study at -- using the month seven data.

Now, I know that HPV infection is -- women remain at risk for HPV infection throughout their life time and so, we decided to evaluate the duration of efficacy of the vaccine over a period of women in a man's life time. This is very important because obviously, for a vaccine to be efficacious, it should have a long term duration of efficacy.

First of all, the vaccine was highly effective and there weren't any break-throughs due to waning immunity, so while we were able to demonstrate that efficacy is associated with the development of high titer anti-HPV responses, we couldn't define a minimum anti-HPV level that protected boys and girls,

women against infection and disease with HPV.

So, all of the efficacy follow-up for duration or the duration of efficacy follow-up will require effectiveness, demonstrations, evaluations of break-through infection. And the longest duration of efficacy that we saw in the current data base, there's more data from after what we submitted to the FDA, but what we were -- the longest duration of follow-up was in protocol five and this was the HPV 16 component of Gardasil. And what you can see here is the anti-HPV levels over time and then -- or the HPV levels and this is the time coordinate. This is when vaccination was done. To note, we had 100 percent efficacy with respect to HPV 16 related CIN, in terms of the prophylactic populations at year four, and what we're doing is comparing anti-HPV levels in the Gardasil group to a group of women who had been previously infected with HPV 16, had mounted an immune response to the infection, cleared the infection and what's left at day zero is the marker of that successful clearance, an anti-HPV level. And among the placebo recipients who were -- who met that criterion, this is the anti-HPV levels, very stable over a prolonged period of time.

Vaccine induced immune responses were higher and they then reached a very stable plateau through month 48, and the same results were observed for the other types. The other types were actually closer to what we saw with the naturally infected women, but again, with a plateau.

So, with 100 percent efficacy at year four and the plateauing of the anti-HPV responses, we're fairly confident that this vaccine -- we're very confident that this vaccine will be -- have long lasting immune protection.

Now, we're not going to stop our evaluation of duration with these data. We specifically have sentinel cohorts, both in adolescents and adults, to evaluate the duration of efficacy. I'll show you the adult population to explain what they are.

We take advantage of an extraordinary health care system in the Nordic region that has centralized all Pap test reporting, all biopsy reporting, in a central data base. There is very high compliance with follow-up here and we can use this very rigorous data base to follow women up for the remainder of their lives.

So, in about 5,500 women in the CIN 2/3 study, we enrolled them specifically in this region and we got their permission to follow them up for the rest of their lives. We've given their identifications to the registries and these women will then be followed for evaluation of long term efficacy, as well as for impact on other cancers.

Now, these women are a sentinel cohort because they were vaccinated in `02 and `03. So, they were vaccinated like -- they already have three years of follow-up. And if we get approval for licensure in the U.S., the first person who will get this vaccine post-licensure, will be some time later on this year.

So, these women will be at least three years ahead of the population who will be generally -- who the general population will become vaccinated post-licensure. And we will be following these women and every two years we'll be getting -- we'll be evaluating for break-through, we'll be typing all of their biopsy lesions, we'll be looking to see whether or not there's any evidence for break-through and we'll be reporting that to regulatory authorities on a regular basis. So, if there is a possibility that we'll need a booster and there's no evidence for that

now, we'll be able to know that well in advance of the general population.

So, to summarize the efficacy data, before I move onto safety, I wanted to -- I think we've demonstrated that prophylactic administration of Gardasil is very effective in preventing cervical and genital disease caused by the four vaccine HPV types. We're already getting a preliminary view that the vaccine reduces the overall burden of disease. Data that were in the original file show efficacy for at least three and a half years. Robust immunogenicity-bridging from adults to children has been shown and we have sentinel cohorts defined for both adults and adolescents that will allow us to look at the long term efficacy and obtain these data before information is needed to make public health policy regarding the possibility of boosters, if such are needed.

So, I wanted to change to the safety evaluation, which was a critical part of our program. Safety was evaluated in a structured approach that was used similarly in all studies. Non-serious adverse experiences were collected day one through 15, post-vaccination, using vaccine report cards for all studies. We collected all serious adverse

experiences, day one through 15 and all serious adverse experiences that occurred at any time during study, if there was the death of a study subject, if it was determined by the investigator to be possibly, probably or definitely either vaccine related or procedure related.

Every visit had a mandatory work sheet that was required to be completed to ensure that no serious AE's went unreported.

We also collected medical history at every visit to capture any events that didn't meet the AE categories. The other key thing is, we had a very comprehensive pregnancy evaluation that I'll describe a little later. A data safety monitoring board was used to supervise phase III studies, as well as now on-going phase III studies.

Now, there 27,004 women in the overall study population. About 5,500 of them received either monovalent vaccine or quadrivalent vaccine formulations, other than Gardasil. We provided separate analyses to FDA of these data. The results are very similar to what I will show for Gardasil itself and the Gardasil itself population was 21,400 subjects. In all of these women we recorded serious

adverse experiences, pregnancy outcomes, new medical history. We had a sub-set of the population, the detailed safety population, in which vaccine report cards were used. In certain sites in protocol 15 non-serious adverse experiences were reported using spontaneous reporting rather than VRC.

This is the summary in the general population of SAE, serious adverse experiences, deaths and discontinuations. There were more subjects in the Gardasil group compared to the placebo group, so the comparisons should be done on a percentage basis. The incidents of serious adverse experiences were comparable. Serious adverse experiences that were thought to be vaccine related were rare. Few women died. The most common cause of death in the program was motor vehicle accident. Discontinuations were very rare, as were discontinuations due to adverse experiences.

These are the seven serious adverse experiences that were judged by the investigators to be possibly, probably or definitely vaccine related. They represented a diversity of different disorders. We typically worry about allergic phenomenon for vaccines. There was one broncho spasm in the Gardasil

group and one case of hyper-sensitivity in the placebo group. Other than that, there were a variety of different things that women reported, very different, one from the other.

Looking at the detailed safety population, now drilling down to non-serious adverse experiences. You can see, again, that there are more Gardasil subjects than placebo subjects, so we look at this on a percentage basis.

There were slightly more adverse experiences in the Gardasil group and this was because of injection site adverse experiences. These injection site adverse experiences were generally mild to moderate in intensity and were generally short lived. Systemic AE's were comparable. Again, comparable serious adverse experiences and very rare discontinuations.

Subjects were required to measure their temperature four hours after receiving a vaccine and then over the next four days. And in the detailed safety population, these are the results of the temperature measurements. Subjects who received Gardasil had a slightly higher rate of fever. This was mostly low-grade fever. When it came to high-

grade fevers, the results were comparable.

We also wanted to compare the adverse experience profile in children versus adults, and so, this a summary of that. These are all -- all of these subjects have received Gardasil and the comparator is women and we're looking at what the adverse experience profile are in the girls and the boys. You can see that the adverse experience profile was comparable between the vaccination groups -- between the different demographic groups. They were slightly less adverse experiences in the children compared to the adults.

And I want to now focus on pregnancy outcomes. This was a unique feature of this program because this vaccine is going to given to women of child-bearing potential. And in our clinical program, we required women to under-go urine pregnancy testing because the vaccine hadn't been tested in pregnant women. And if the urine pregnancy test was positive, then they weren't vaccinated. But never the less, there some inadvertent -- we knew that there would be some inadvertent exposure during pregnancy and so, we set out to ensure that all pregnancy outcomes were carefully evaluated.

In particular, we got medical history during pregnancy in all these women. We evaluated the outcomes in both mom and the child through the neonatal period, but also we followed all the infants over the course of the years because we wanted to make sure that anything that wasn't picked up during the neonatal period could be picked up later on.

Causes of spontaneous abortions were evaluated. In other words, we tried to get the reason why the spontaneous abortion occurred and determined why a women underwent elective abortion, if that's what she chose.

Now, our program included screening for pregnancy and in studies that look at screening for pregnancy, the rates of spontaneous abortion are around 30 percent. Congenital anomalies typically occur in three to four percent of live births and that's -- these data are provided to you as sort of a framework from which you'll see what the results in the clinical program were.

These are the pregnancy outcomes as of the safety update report that was presented to CBER on 11, November 2005.

There were a total of 1,115 women --

1,151 women who had a pregnancy. Some of them had multiple pregnancies or twins. And so, there were more pregnancies than there are women with pregnancies. The number of -- about 500 pregnancies were still ongoing or whose outcome was unknown over the course of the -- at the time of the cut-off for the safety update report. Ninety percent of these pregnancies were pregnancies that were ongoing. There were very few pregnancies whose outcome was unknown. So, there were about 2,000 pregnancies whose outcomes were known. Live births and fetal losses were comparable between the two vaccination groups.

Early on in the phase III program the Data Safety and Monitoring Board had asked that we divide out the pregnancies by those whose onset was in close proximity to vaccination and those whose estimated onset of pregnancy was further away from the timing of vaccination. And they used -- they asked us to use a 30 day number.

And so, we presented -- we did all of our analyses looking at fetuses or infants with known outcomes, estimated onset of pregnancy within 30 days of vaccination or beyond 30 days of vaccination.

And if you look at the Gardasil and

placebo groups, there was slightly less spontaneous loss in the Gardasil group compared to placebo. Slightly higher live birth rate compared to the placebo. Again, looking at beyond 30 days, comparable rates of spontaneous loss, slightly lower elective terminations, slightly higher live birth rates. So, those numbers were comparable.

Overall, congenital anomalies were also comparable. Fifteen cases in the Gardasil group, 16 cases in the placebo group, representing a rate of about 2.2 percent of live births.

Looking at the estimated onset of pregnancy within 30 days of a vaccination and beyond 30 days, there was a difference in the patterns between the vaccination groups. So, there were five congenital anomalies whose estimated onset was within 30 days of the vaccination and all five were in the group that received Gardasil. On the other hand, when we look at estimated onset of pregnancy beyond 30 days of a vaccination, we saw that there were much fewer in the Gardasil group compared to the placebo group, six fewer here.

When we looked at the five congenital anomalies that occurred in the group that received

Gardasil within 30 days, we noted that there were five very diverse kinds of congenital anomalies, most of them were very common lesions. We evaluated the timing where the very earliest period that might be where injury might occur, that might result in these congenital abnormalities would be, and you can see that the timing of these were very different from the timing of exposure. For example, second trimester versus one day, eighth week versus 19 days, very different timing.

And so, on the basis of this diversity of congenital anomalies, the fact that the overall rates were comparable, the facts that are pre-clinical developmental, reductive toxicology studies, were all negative at doses much higher than given to humans and with the help of a broad panel of teratology experts who looked at this in a -- panel of four teratology experts who looked at this in a blinded way and then in an unblinded way, the overall assessment was that this was not - highly unlikely to be related to Gardasil and the findings were most likely a chance finding.

Now, safety is an important component of studies looking forward. We have a large post-

licensure study in 35,000 subjects to evaluate general safety and pregnancy outcomes, a registry to monitor for pregnancy outcomes because women are -- this is a vaccine to be given to women of child-bearing potential. And then we have two large long term evaluations that will evaluate not only safety, but also effectiveness.

The first is the Nordic cohort that I spoke about, but then the second is, is another collaboration we've initiated with the Government of Norway. They are going to use their wonderful cervical cancer infrastructure where they capture every single Pap test and biopsy in the country, to also capture every single HPV vaccination in the country. They are going to mandate that everyone get registered who gets the vaccine. And on the basis of that, we'll be able to look at both safety and efficacy outcomes over the long term in this country.

So, from a safety perspective, we conclude that Gardasil is generally well tolerated in this age range. We did see an increase in injection site adverse experiences compared to placebo, as well as low-grade fevers. Very rare discontinuations due to an adverse experiences. Data I didn't have time to

show you, was that the vaccine is well tolerated in women who are positive to one HPV type, so they're already infected with at least one type. Pregnancy outcomes were thoroughly evaluated and appeared to be comparable and we have a large pharmacovigilance program that is going to be launched once we obtain licensure and agreement with FDA.

So, finally, I wanted to conclude with describing the overall benefit risk profile for Gardasil. Earlier on in this presentation, I told you that we described the burden of HPV infection and disease. There are 35,000 cancers in the U.S. that are caused by HPV every year. Twenty-five-thousand are caused by 16 and 18. One point four million cases of CIN annually. Seven-hundred-thousand caused by the four HPV types. A million cases of genital warts, 900,000 caused by vaccine types. Six-thousand cases of RRP, 5,400 caused by vaccine types in both men an women, boys and girls.

We've shown that the prophylactic administration of Gardasil is highly efficacious. This vaccine would provide, when given to women prior to exposure, is highly effective in preventing cancers, pre-cancerous lesions, external genital

lesions targeted by the vaccine HPV types. The results were consistent across and within studies and in the per-protocol and in the HPV naive populations.

We are already beginning to see the benefit of the vaccine with respect to population impact. Reductions in the overall burden of CIN, CIN 2/3, external genital lesions. These are preliminary analyses. The final analyses will be provided at the end of the phase III program next spring.

We have evaluations and long term efficacy of the vaccine. We know we have efficacy through three and a half years. No break-throughs due to waning immunity. Other studies, more recently, have been un-blinded, that have shared data on this. Sentinel cohorts will be used for follow-up well ahead of the general population and I didn't have time to talk about it, but we have a sentinel cohort for adolescents as well.

Our safety profile -- the safety profile of Gardasil is favorable. Rarely do individuals discontinue due to any adverse experiences. We have thoroughly evaluated pregnancy outcomes and we have further pharmacovigilance work that will be done in the immediate post-licensure period.

I wanted to take a moment and talk about nine to 15 year old boys in the clinical program. What we saw in the clinical program was that the vaccine was highly immunogenic and well tolerated in this group and by virtue of the fact that we saw efficacy for external genital lesions, lesions that are comparable between the genders, caused by the same HPV types, same response to therapy, we feel that the efficacy of the vaccine is highly likely to be present in males.

We are interested in facilitating the possibility of public health authorities considering vaccinations of males right from the beginning of the post-licensure period. And the reason for this is that there is strong public health rationale for vaccinating boys and a cost to delaying the vaccination of boys.

Vaccine coverage in girls is going to be incomplete. This is a hard age range to target. It's going to be some time until we get high coverage rates. We know that men transmit HPV to women and we know from previous experiences using two kinds of -- two vaccination programs that when you try to target vaccines to a particular population, you can't

eradicate the disease very well, compared to universal vaccination. And the particularly relevant example, at least from my perspective, is rubella, where female only vaccination failed to eradicate congenital rubella syndrome. It required gender-neutral vaccination.

And so -- and we've also shown in our clinical -- in modeling work that if you delay a vaccination in boys, you will reduce the overall population efficacy of the vaccine, you will delay the time until the maximum reduction in cervical cancer that you could expect.

And so, form our perspective, we would like to be able to propose labeling that would allow flexibility and decision making for groups that are really going to make vaccination policy in this country, to evaluate whether gender-neutral vaccination should be used or female only vaccination, based on their read of the data.

So, our proposal is that we would provide all the information that we have generated to date, the efficacy in the diseases at which efficacy was shown, and of course, inclusion of all immunogenicity safety data in girls, women and boys.

So, I'll conclude by saying that the benefit risk profile for Gardasil is highly favorable. We've shown that the vaccine prevents a very important set of public health problems, cervical, vulvar and vaginal cancer, cervical pre-cancers and external genital lesions. The vaccine has an excellent safety profile and this is a very important disease for this country and vaccination will really reduce the burden of HPV disease, so it will have a large, positive public health impact.

I wanted to thank you for your attention and I'll be glad to answer any questions, if there are any.

DR. FARLEY: Thank you, Dr. Barr. It looks as if we have, perhaps, about 15 minutes if you wanted to go ahead and take this time to ask a few questions. We will have more time this afternoon for further discussion and later this morning after the FDA presentation. But I'll open it right now to questions from the panel, and it looks like Dr. LaRussa can start.

DR. LARUSSA: Hi. I have a few questions about immunogenicity. I was unclear about your statement about not being able to find a protective

cut-off for antibody titers. So, I wanted to know if in your populations that got less than one dose -- less than three doses of that vaccine, were you able to look at antibody titers in those that did and did not come down with disease?

And then the second question is about, did you look at any other surrogate markers for protection?

And finally, the third question is about boosting of antibody titers due to exposure to HPV?

DR. BARR: Okay. Well, I'll take them in order. The first point has to do with whether or not we have any data in people with less than three doses, and unfortunately, compliance was really high. We had like 20 or 30 people who got less than two doses and continued in the study. So we didn't really measure -- we weren't able to measure efficacy in this population, not enough people.

The second question that you had about is there any potential other surrogates, and the answer is no. We think that immunogenicity and immune-memory are really critical.

And the third question has to do with boosting, and that's actually data that I'd like to

share, if I could, for a couple of seconds.

First of all, I wanted to point out that the vaccines efficacy is now -- we've evaluated boosting, and that's what I'm going to share with you. We've evaluated the vaccines efficacy now for five years and we had the evaluation of efficacy through five years, just recently unwinded. And if I could have slide 247, please.

Okay. So, we looked at efficacy now through five years of follow-up and what you can see is that the vaccine's efficacy remained high, 96 percent. There were two cases in the Gardasil group, this is in Protocol 007, by the way, our immunogenicity and long term efficacy trial, phase IIB study.

And what we were able to see, there were two cases in the Gardasil group, 46 in the placebo group. These two cases were an early infection and then a single time detection at the last visit on record. So, these were infections -- this was not a confirmed and persistent infection, but it was an infection that was -- a single time detection of the last visit on record. So, through five years, we've got a high efficacy.

If you take slide 248, please. When we look at the anti-HPV levels, again, these are baselines seropositive, PCR negative people. These are women who have been infected, cleared their infection, mounted an immune response and now have excellent -- have residual anti-HPV and got placebo. You can see that anti-HPV levels are very, very high and continue to be high at month 60, much higher than what we see in infected people. But the key thing here is the stability of the immune response. So, efficacy, without waning immunity over here, both with immunogenicity and efficacy.

Now, boosting. Next slide, 376, please. To examine the notion of whether immune memory was demonstrated, we didn't think we needed a booster at five years, but we did an immune memory evaluation because we wanted to evaluate whether this vaccine can create the kind of memory that's a hallmark of long term protected efficacy.

So, we looked at -- we gave a fourth dose, a booster dose at year five, among women who received Gardasil. So, they received a three dose of Gardasil, and then a booster -- a fourth dose at year five, to challenge whether we could demonstrate immune memory.

And what you can see is that anti-HPV responses for 16 and 18, six and 11, was the same, much, much higher, even at one week and one month post-dose -- post-fourth dose compared to the month seven results.

So, we have very high boostability, long term efficacy through five years and obviously, a generation of robust immune memory.

DR. FARLEY: Dr. Emerson.

DR. EMERSON: If I could just follow-up. On your slide 248, you remarked that those women had all cleared the virus. And so, is it -- can we infer from that that level -- that a titer that they have is protecting them from repeat infection?

DR. BARR: It's hard to tell because the -- these women are generally protected. So, when we looked at our phase III program where we had quite a few women who were seropositive and PCR negative, the event rate was definitely lower in that group, but it wasn't zero. It was like 80 percent less than what we would -- the comparably naive population.

So, I think that these women are generally protected, but they're not fully protected. That's the best that we can do.

DR. FARLEY: I have a couple of questions.

Can -- you mentioned that about 70 percent of the cervical cancers can be attributed to the 16 and 18, but then you used 55 percent as your calculator, and I guess that was based on the experience within this study, and why do you think there was that difference? Do you think that reflects variation in the trends over time?

And also, when you were evaluating these patients, were they -- each one evaluated for the possibility of asymptomatic, if they had no lesions, no abnormalities, were they evaluated for asymptomatic carriage or the presence of the virus? Is that a phenomena that exists? And I guess I'm thinking that Dr. LaRussa was wondering about natural boosting, whether exposures to the presence of the virus was serving or would serve as natural boosting?

DR. BARR: Okay, let me address them one at a time. The 55 percent number was for CIN 2/3 and the reason why we had a higher -- CIN 2 and CIN 3 have different proportions of HPV 16 and 18 association. So, for example, CIN 3 is much higher, because it's just right before cervical cancer, much more 16 and 18 related. CIN 2, a little bit more of a heterogeneous mix of disease and so, it has slightly lower

association.

And so, it really represented that mix. When we looked the -- just looking at CIN 3 alone, we were at the 70 percent mark.

So, I think it was just an artifact of the mix of the two lesions.

The question that you asked about asymptomatic carriage -- right, that was the next -- were there three questions or two? Asymptomatic carriage, okay, sorry. We had looked at infection as an end point in the phase II studies. And so, we looked at infection for up to four years of follow-up. Some of the women were "asymptomatic", because they didn't have a Pap test abnormality and the vaccine prevented those infections as well.

There was no evidence for natural boosting from the presence of exposure, for example, to HPV. It's hard to measure that because we don't -- we didn't test the partners to see whether, let's say, the partners were introducing HPV to them. They weren't getting infected because they were vaccinated, but they were seeing the virus and maybe get exposure. So, we don't know and natural history studies haven't really shown whether you have this kind of auto-

boosting phenomena. It's something that still needs further evaluation.

DR. FARLEY: Dr. Markowitz.

DR. MARKOWITZ: I have a question about slide 66. In that slide you're showing the efficacy against external genital lesions. And in some of the other tables you had broken it down by specific pathology, but you haven't here. How many of these cases were genital warts versus VIN or VaIN?

DR. BARR: Okay. Let me -- I want to see the break-out. I'm going to show you the break-out of external genital lesions in the population.

Let's see, okay, yes. Can I see slide 854, please? And I'm going to show you just a couple of slides.

If you wanted to -- if you looked, what you see here is that they were -- now we're breaking down to condyloma, vulvar condyloma, vaginal condyloma. These are -- this is in the entire population of the per-protocol group. So, 91, 88 and eight vaginal, vulvar condyloma. You can see that the condylomas were overwhelmingly, six and 11. Where there was 16 and 18, they were carried along with six and 11 in most cases.

Eight-fifty-five, please, 855. VIN 1, VIN 2/3, high efficacy, and we can see there were 10 cases. These were all six and 11 related. There are low-grade. VIN 2/3, again, strong 16 and 18 contribution and this is, again, for protocol population. Next slide.

And finally, VaIN, and you can see that there is a variety of different lesions and VaIN 2/3, all 16 and 18 related in this protocol population. Thanks.

DR. FARLEY: Dr. LaRussa, one more time.

DR. LARUSSA: Just one more follow-up question. I'm trying to figure out how you could separate out the natural boosting phenomenon and I guess what makes me wonder about that is that the antibody titers in the placebo group remain stable over a very long time period and don't really decline over time. So, maybe that is going on, but you may not be able to figure it out until the epidemiology of the disease changes.

DR. BARR: Yes, we don't know. I mean, I think that the stability might also be a marker of presence of immune memory. So, it's a good question. I don't have any further data on that, unfortunately.

DR. FARLEY: Dr. Greene.

DR. GREENE: I had two questions. First, one is, were the subjects who participated in the study paid or compensated in any way? And the other question is, what can you tell us about any interaction between cigarette smoking and vaccine?

DR. BARR: Subjects were -- all of the issues about subject payment were subject to the local rules and regulations, both in the United States and ex-U.S. In most countries around the world, subjects were not paid because that's not allowed. In the U.S., there was a compensation for time spent in the study. All of that kind of interaction in terms of payment was to be approved by the Institutional Review Boards of each participating study site.

In terms of cigarette smoking, we did -- about a third of the subjects smoked and we saw, obviously, high prophylactic efficacy. Some of the women who tended to be cases were more likely to be smokers. So, in other words, particularly with vulvar disease, there seemed to be more enriched for current smokers.

DR. FARLEY: Dr. Emerson.

DR. EMERSON: This is back to the question

of, sort of the 70 percent of cancers that are due to 16 and 18. And I guess I'm asking is, what's our criteria and what's our evidence for attributing an individual's cancer to a specific type -- and here what I'm wondering about is, distinguishing that from sort of an opportunistic environment in a cell undergoing a pre-malignant transformation that might select for certain virus types appearing in the cells and lesions?

DR. BARR: So, just -- first of all, I want a quick clarification, how do we know that that was the type that actually caused the cancer? Is that it?

Okay. So, the reason we knew that was the type that caused the pre-cancerous lesion was because we did this thin section PCR analysis. We tried to get as close as possible to the point of, here's the cell and here's the virus on top of it.

Now, we tried to use florescent in situ hybridization, which allows you to actually look at the cell and see the lesion, but the sensitivity wasn't high enough. So, we used PCR to evaluate exactly adjacent blocks, and that's probably as tight as you can get, in terms of the associations. In terms of HPV 16's role in causing that lesion, HPV 16

has been demonstrated to be -- you know, the associations between HPV 16 and CIN 2/3 are very -- and cancer, of course, are very, very tight.

DR. EMERSON: But I guess what I'm talking about is just the fact that you're seeing the virus in the cell, is that possibly related to the pre-malignant transformation being more -- allowing the infection more and this occurring after the pre-malignant transformation that we're seeing, and this has relevance in terms of whether those results in terms of seeing enough of the population effect is going to pan out to really be that same 70 percent.

DR. BARR: Right. Well, I see what you're saying. So, first of all, the number -- that 70 percent value is uniform around the world in different ways in which people are looking at that number, both in terms of looking at cancers and really focusing in on those kinds of lesions. So, that's the best that we can do in terms of associating HPV 16 and cancer.

We have -- we also know that HPV 16 is possibly the strongest predictor for cervical cancer. And so, in terms of associating this virus with this lesion, we came to the closest that we could and developed the techniques that would make it a highly

sensitive approach of comparing the two. That's the best that we were able to do.

There was -- there isn't any marker that says, you know, okay, here's an HPV 16. It is glomming right onto the cell and causing it to be malignant, if you know what I mean. Just the strong associations between these things and the fact that persistent HPV 16 infection is highly likely to cause disease and the association with 16 is particularly relevant for cervical cancer, 18 for adenocarcinoma and so on.

DR. FARLEY: Dr. Wharton.

DR. WHARTON: Can you share any information with us about the adverse events you observed in the dose ranging study?

DR. BARR: Yes. So, in the dose ranging study, where we -- we looked -- the three doses that we chose were, for better -- ease of use, is low, medium and high. We chose the low for Gardasil. In medium and high we had a slightly higher dose response with respect to injection site adverse experiences and low-grade fever.

So, what we found is the anti-HPV levels were comparable between the three doses and we saw

this AE gradient in about 270 subjects per group. So, we figured probably it's real and that's why we chose it, 20, 40, 40, 20.

DR. FARLEY: Dr. Unger.

DR. UNGER: Could you comment on the kind of PCR assays that you were using for your typing studies?

DR. BARR: Yes, we were using PCR assays that evaluated for three genes, the L1, the E6 and the E7 genes for -- of each individual virus and that was -- the reason for this was because we wanted to make sure that we had -- that we were highly sensitive in detecting every type. So, you know L1 sometimes disappears in high-grade lesions, and that's why we chose the E6 and E7. The sensitivities of the assays were really high.

DR. UNGER: Did you do them as type specific assay formats, or was it consensus kind of?

DR. BARR: No, it was type specific assay formats, each type on its own. That's why it's taking us so long to do all the other types.

DR. FARLEY: Why don't we take one more question, Dr. Royal, and then we'll move to our break.

DR. ROYAL: In looking at the broader

consequences of the immunization, did you see any changes in incidents of other types of infections or STD's, either related to changes in immunity or behavior, sexual behavior?

DR. BARR: No. A couple of things, we didn't see any changes in sexual behavior between the two -- in the study over the course of time. In fact, the rates of sexual behavior -- I mean, the number of new sexual partners declined over the course of time.

In terms of changes in the rates of chlamydia and gonorrhea and all the others, we did test for all of that. The rates were comparable between vaccination groups and also between, compared to what the general population -- or expected event rates of clinical studies that have looked at these particular pathogens.

DR. FARLEY: Thank you very much. I think we'll have other opportunities to ask more questions later. Why don't we take a 15 minute break and return just after 11:00, a few minutes after 11:00. Thank you.

(Whereupon, the foregoing presentation recessed briefly at approximately 10:50 a.m.)

DR. FARLEY: Thank you. We're going to

move onto our next section. Our last speaker for the morning session will be Dr. Nancy Miller, representing FDA and giving their perspective on this new product. Thank you.

DR. MILLER: Good morning. My name is Dr. Miller and I'll be presenting the FDA review of the VLA Gardasil.

I'd just like to thank all the members and acknowledge all the members of the review team that were involved in this very complicated application review and accomplishing it in a priority basis.

Gardasil, as Dr. Barr had noted, is a recombinant vaccine, the vaccine that is prepared from purified virus-like particles of the major capsid L1 protein of HPV 6, 11, 16 and 18. The L1 proteins are produced by fermentations in recombinant Saccharomyces cerevisiae, and self-assembled into the virus-like particles that were shown and they are purified and absorbed onto aluminum. Each 0.5 mL dose contains 21 micrograms of HPV 6 and 20 micrograms of HPV 18 and 40 micrograms each of HPV 11 and 16. The vaccine is administered intra-muscularly on a zero, two and six month schedule.

The applicants proposed indications are as

follows: they include the prevention of HPV 16 and 18, related cervical cancer, cervical adenocarcinoma in situ or AIS, cervical intraepithelial neoplasia, grade 2 and 3, CIN, vulvar and vaginal cancer, vulvar intraepithelial neoplasia grade 2 and 3 and vaginal intraepithelial neoplasia grade 2 and 3. They are also the indication -- proposed includes prevention of HPV 6, 11, 16 and 18, related CIN grade 1, genital warts or condyloma acuminata, vulvar intraepithelial neoplasia grade 1 and VaIN grade 1 and HPV infection.

The sponsor's proposed indication also includes the population of children and adolescents, nine through 17 years of age and women 18 through 26 years of age.

The FDA considers the data submitted in the BLA to be supportive of use of Gardasil in pre-adolescent and adolescent females nine to 17 years of age and females 18 to 26 years of age.

I just wanted to go briefly through the regulatory history. This first IND, or investigational new drug application, for the monovalent 11 vaccine was submitted in 1997 and the other IND's for the monovalent product 16 and 18 soon followed.

In 2000, the IND for the quadrivalent vaccine was submitted and in November 2001, was the important VRBPAC discussion of end points that would be appropriate for phase III development of a preventive HPV vaccine.

In 2002, product development program was granted fast-track status and phase III trials were started.

In May of 2005, we had our pre-BLA meeting, with an agreement to allow rolling of the BLA and a priority review.

In August of 2005, the BLA began rolling. The first part was submitted and in December 2005, the last section of the rolling BLA was received, including phase III study data and that was the start of a six month priority review.

The efficacy end points for preventive HPV vaccine were discussed at the November 2001 VRBPAC and it was decided that CIN 2/3 histology, AIS or worse, with virology would be appropriate because these entities are immediate precursors to cervical cancer and adenocarcinoma, as well.

And cervical cancer was not feasible as an end point because of the long time to development and

because the standard of care removes -- involves removing or excising CIN 2/3.

In brief, there were four phase I/II studies that studied the monovalent vaccines. They were as follows: 001 for 11, 002 for 16, 004 also for 16 and 006 for 18. That studied the safety and immunogenicity of those particular monovalent vaccines.

The phase III studies included -- which contributed to the assessment of efficacy included the following: protocol 005 was a proof of concept phase II efficacy trial that involved HPV 16 vaccine. Protocol 007 was a phase IIB study to assess the dose for the quadrivalent HPV vaccine to go forward into phase III trials and to assess the efficacy for prevention of infection caused by the four vaccine HPV types.

Protocol 013 was a phase III study that was to assess the efficacy of the quadrivalent vaccine against CIN and warts. And protocol 015 was a phase III study to assess the efficacy of the quadrivalent vaccine for CIN 2/3 associated with HPV 16 and/or 18.

And protocol 015 included a consistency lot sub-study, non-serious adverse event study and

there is going to be a continuation of the registry study.

Gardasil was also studied in protocol 013 in two sub-studies. Protocol 011 was a hepatitis B concomitant use sub-study and 012 bridged the results or immunogenicity results from HPV 16 and 005 to the HPV component of the quadrivalent vaccine.

Protocol 016 was designed to evaluate the safety and immunogenicity of the vaccine in pre-adolescents 10 to 15 years of age, with comparison of the immune response between the younger age group of subjects, to women 16 to 23 years of age. In addition, this protocol included a sub-study to assess the immunogenicity of partial dose formulations.

Protocol 018 provided additional safety and immunogenicity data for the pre-adolescent/adolescent age group, down to the age of nine years of age and with a comparison to a true saline placebo.

Cases of HPV 16 and/or 18 related CIN 2/3 were pooled from those four studies, 005, 007, 013 and 015 and these studies were very similar in design. They were all double-lined, randomized, placebo controlled, they were all international, except for

protocol 005, and visits were generally every six months, except for protocol 015, where there was yearly follow-up, except for the first year.

The efficacy trials were conducted in females 16 to 23 years of age in 005, 007 and 013 and up to 26 years of age in protocol 015 to accommodate subjects in Singapore. Lifetime partners were to be less than five and subjects were allowed -- with a history of abnormal Pap smear were not allowed into the trial. But however, the first day that they had a Pap smear, if it was abnormal, they were not excluded from study participation.

The Pap tests, again, this shows that the interval is every six months, except for 015, which was usually 12 months, except as indicated by the algorithm and the minimal Pap test for referral to colposcopy was atypical squamous cells of undetermined significance. And there was also a mandatory colposcopy algorithm for 013 and 015.

This slide just details the differences in the colposcopy algorithms for the four trials. It is noted that the protocols all had a well defined triage scheme for referral to colposcopy and ascertainment of abnormal Pap tests.

The cases were determined based on reading of an expert pathology panel who were blinded to PCR status, central lab diagnosis and other Pap panel diagnosis at the time of reading, in conjunction with identification of the virus -- HPV type by PCR in tissue, adjacent to the histo-pathologic tissue.

The PCR assay was performed in paraffin blocks for 007, 013 and 015 and frozen biopsy in 005.

The median age of the subjects for the efficacy population was 20 years of age. The number of subjects who received dose of vaccine or placebo in each trial are noted in the slides and protocol 015 is the largest trial and protocol 013, next largest.

In protocol 013, an additional 304 subjects also received the HPV 16 monovalent vaccine for that 012 sub-study.

The mean duration is also of importance. Protocol 005, at the time of the BLA submission, median duration of follow-up was 3.1 years, 007 was 2.4 years, protocol 013 was 1.7 years and protocol 015 was 1.4 years.

This slide shows the distribution of subjects in the efficacy population across the four geographic regions that were included in the trial.

The majority of subjects in protocol 015 were from Europe and the majority in 013 were from Latin America. But there is a distribution among all of the four groups, the four regions.

And this -- some subjects were excluded from the per-protocol analysis for HPV 16 and/or 18 because of baseline HPV status.

Now, I'll just go over one of these slides. For example, we wanted to just go over how a case was counted. If a subject was naive, that is, did not have presence of antibody to that particular HPV type that was in the vaccine and was PCR negative from day one through month seven, they would be included in this specific per-protocol population. And this example shows a subject who is not naive or had evidence of previous 16 exposure, but could still be included in the per-protocol analyses -- populations for 6, 11 and 18.

It is also important just to understand the different efficacy analysis populations that we used. The per-protocol population for efficacy had received all vaccinations, three vaccinations, they were naive to relevant vaccine HPV type through month seven, did not deviate from protocol and cases were

counted after month seven.

The modified intent to treat population one was -- very similar to the per-protocol population, but included protocol violators.

The MITT-2 or modified intent to treat-2 population received at least one vaccination, was naive to the relevant vaccine HPV type at day one and had any follow-up visit after the first vaccination. Cases were counted from 30 days after dose one. So they again were naive to the specific HPV type at day one that you were analyzing.

The restricted MITT-2 population, they were seronegative and PCR negative to all four vaccine HPV types at day one and had a normal Pap test at day one. Cases were counted 30 days after the first dose.

And then, there was an all MITT-1 population, they were naive to all vaccine types through month seven and cases were counted starting after month seven. Again, they were naive, again, to the four vaccine types.

The modified intent to treat-3 population, this we considered important. They included all subjects, regardless of baseline HPV status. These subjects received at least one vaccination and had any

follow-up visit one month after dose one and cases were counted from 30 days after dose one. Again, they were included regardless of the baseline HPV status.

And the baseline characteristics of the subjects in the efficacy population show that 12 percent had evidence of squamous intraepithelial lesion, present at baseline and most of these were the atypical squamous cells of undetermined significance in the low-grade squamous intraepithelial lesions. And 27 percent were PCR positive and/or seropositive to a vaccine HPV type. Eleven percent were seropositive for 16 and eight percent were seropositive for six, about four percent for 18 and about two percent for 11 at baseline.

The end points from the efficacy protocols included HPV 16, 18, related CIN 2/3 or worse, and that was the primary end point in protocol 015, as well as the pre-specified combined analysis.

HPV 6, 11, 16, 18, related CIN and 6, 11, 16, 18 related external genital lesion end point were our co-primary end points in protocol 013, but were also assessed over the combined trials.

Other end points of interest included HPV 16 and 18 related external genital lesions, CIN 2/3

due to any HPV type and non-vaccine HPV types and external genital lesions, also due to any HPV type and non-vaccine HPV types.

First, I'll just discuss the efficacy against HPV 16, 2/3 or worse. In the per-protocol population, as noted in protocol 15, there was 100 percent efficacy, 21 case of placebo, none in Gardasil.

We looked at the MITT-3 again, because we felt it important. There were all comers, regardless of baseline HPV status and what might happen in the general population, and there was a 39 percent efficacy in this specific population, and that's for 16, 18, related CIN 2/3 or worse.

The analysis of this efficacy across those protocols, 005, 007, 013 and 015 were just about the same, 100 percent in the per-protocol population and approximately 39 percent in the MITT-3 population.

In the analysis of the combined trials for vaccine efficacy against specific HPV types, and we looked at the MITT-3 population, because again, these were all comers, there appeared to be better efficacy against HPV 18 related CIN 2/3 or worse, as compared to HPV 16 2/3 or worse. And it's no -- it has been

reported that HPV 16 has a higher rate of progression noted than other types, but there wasn't any real difference to time of disease with these two types. So it's unclear of what else might be operative besides -- prevalence of disease doesn't seem to account for everything.

The efficacy against HPV 6, 11, 16, 18 related CIN is next shown. And again, we looked at both the per-protocol population with 100 percent efficacy against all type of CIN, CIN 1, 2, 3 that are associated with the vaccine types and in the -- and also, at the MITT-3 population of people, again, that were admitted -- in the trial, regardless of baseline status. In that population, there were -- 43 percent efficacy was noted.

Across trials we see, for the 95.2 percent efficacy, for 007, 013 and 015 and it's noted that there were four cases in the per-protocol analysis in this combined trial. But again, these were all four cases that occurred in protocol 015 and they all had CIN 1 related to HPV 16 that developed at month 12 to 13.

When vaccine efficacy against vaccine HPV types for the related CIN is assessed in combined

trials, the vaccine efficacy against HPV 16 related CIN lesions, 70 percent is higher than compared to the vaccine efficacy for 16 related CIN, 46 percent. Again, we're looking at the MITT-3 population, again, the all comers. For 6 and 11 it's approximately 74 percent.

One of the potential concerns identified by the review team was the apparent increased incidents of CIN 2/3 or AIS related to the vaccine type with which a subject was originally infected in the Gardasil recipients who were PCR positive and seropositive at baseline for that specific HPV type.

This reversal was not seen in the other non-naive groups, meaning, not in the seropositive, PCR negative or in the PCR positive, seronegative. And there was a further analysis to see if there was any difference. It is noted that the non-naive subjects in the Gardasil group who developed a case were 121, as compared to 130 in the placebo group.

When selected characteristics for this sub-group of vaccine related HPV PCR positivity and seropositive subjects were evaluated at day one, this was especially seen in protocol 13. It was noted that a higher percentage of subjects in Gardasil group had

baseline Pap test that was high-grade -- high squamous Intraepithelial lesion, as compared to placebo where there was 3.7 percent. And after sub-group analyses making conclusions from that kind of analysis was also fraught with danger, but we wanted to -- we felt that after evaluation of these background characteristics, there seemed to be a reasonable explanation for the results and were not likely indicative of enhancement of disease.

The efficacy against any HPV type is also of important -- and non-vaccine HPV types, because 16, 18, 6 and 11, although they are -- do represent high proportion of number of cases. There are other HPV types that are -- that a subject may be exposed to.

The overall impact on CIN 2/3 or worse, due to any HPV type, again, this is in all comers, whether they are regardless of baseline status, was 12.2 percent.

When you look at the efficacy against HPV types not included in the vaccine, again, we don't know the exact types because these data are for the specific non-vaccine HPV types that have not yet been submitted to the BLA. We see that for CIN 2 and CIN 3, there does not seem to be any efficacy and there

are a somewhat higher number of cases in CIN -- in the Gardasil group, as compared to the placebo group.

Now, we'll discuss the efficacy against HPV 6, 11, 16, 18 related external genital lesions. And in protocol 13, this was a co-primary end point. In the vaccine efficacy against -- in the per-protocol population is again, 100 percent and this is for specific types. In the MITT-3 population, the vaccine efficacy is higher than what we saw for the CIN 2/3 lesions of approximately 68 percent. And there was possible -- there is probably less prevalent disease in this particular efficacy population because subjects were able to -- they were excluded if they had a history of a previous external genital lesion. They would know that, probably more readily than if they had an abnormal Pap smear.

But again, we see that efficacy, and in a similar analysis in the combined trials, we see a very high efficacy in the per-protocol population of 99.1 percent. In the restricted MITT-2, which is naive at day one, to all four types, had a negative Pap smear and cases counted starting from 30 days after dose one, there was also a very high efficacy of 95 percent. And in the all comers population, regardless

of the baseline HPV status, for the external genital lesions related to 6, 11, 16 and 18, efficacy was 70 percent.

When we look at specific HPV types and efficacy against those types, again, there was a higher efficacy in the HPV 18 types. Again, this is the MITT-3 population, all comers and it was 90 percent. For 16 it was 80 percent and for 6 and 11 it was 70 percent.

Now, the vaccine -- we looked at vaccine efficacy also. It was provided for the specific grades, condyloma, VIN 1 or VaIN 1, VIN 2/3 or VaIN 2/3 and that in the per-protocol population was also higher at 100 percent. When you look at the all comers population, we still see substantial efficacy against the low-grade lesions and 70 percent against the higher-grade lesions.

FDA had requested that the EGL's be broken down by specific type with analysis in protocols 13 and 15, as well as in the combined protocols. And in the per-protocol analysis when -- for the condyloma, 98 and 99 percent. For VIN 1, the low-grade vulvar lesion, 100 percent. VIN 2/3, again, this is a per-protocol, 100 percent and VaIN 2/3 as well.

When you look at the all comers population, the efficacy is lower, but 70 percent approximately for the condyloma. VIN 2, again, the confidence intervals are less than zero for the VIN 1 and VaIN 2/3 because of the low numbers and because of the lower numbers of cases that were accrued, it was more difficult to make a conclusion, but it was in the right direction, that's for sure.

This particular slide shows efficacy against 6, 11, 16, 18 related external genital lesions in those non-naive patients, broken down by sero-status and PCR status. And we did not see the imbalance that was seen in the CIN 2/3 cases that we had shown on a previous slide. Numbers were approximately the same. The people -- you know, it really wasn't -- there was five cases in the Gardasil group for the seropositive, PCR positive and five cases in the placebo group as well.

The impact of Gardasil on the incidence of EGL's due to any HPV type, again, that includes non-vaccine and vaccine types, were shown in this slide and for that restricted, that naive population, the restricted MITT-2 population, it ranged from 65 percent to approximately 81 percent, low-grade to

higher-grade external genital lesions, and 41 to 49 percent in the all comers population.

When you looked at efficacy against external and genital lesions, not related to the vaccine or not included in the vaccine, we don't see any efficacy in this population.

Now, we'll just discuss the safety findings. Just to go over, there was the detailed safety population where vaccine report cards were used and general safety population where SAE's were collected. This shows the vaccine exposure in nine to 15 year old female subjects from protocols 016 and 018 and that included about 1,100. The safety surveillance and the detailed safety cohort included vaccine report cards for 14 days after each vaccination, including 005, 007, 013 and the non-serious adverse event sub-study of 015. These included solicited local adverse events, pain, tenderness, redness for five days after vaccination, temperatures for five days after vaccination greater than or equal to 100 degrees and solicited and unsolicited systemic adverse events, which included sore muscles, sore joints, headaches, rash, diarrhea for 14 days after each vaccination.

Serious adverse events, any SAE or serious adverse event from the day of consent to 14 days post-dose one and 14 days post-dose two and three, regardless of attribution, any death or SAE which resulted in study discontinuation, any SAE throughout the study which was possibly vaccine or procedural related or whose relationship was unclear and pregnancy related SAE's were followed throughout the study.

New medical conditions were also reported, all in the pre-vaccination, in the study period through month seven and the study period after month seven. Again, all pregnancies were to be followed to outcome. SAE's were reported for mothers and infants and lactation outcomes were followed as well.

These are the safety results. Across all trials for the studies, there were 11 deaths in the Gardasil group or 0.9 percent and in the placebo group there were seven or 0.7 percent overall. No discernable pattern was identified. We looked at serious adverse events across the study. The total numbers -- percentages, 0.9 percent of the Gardasil and 1 percent in placebo were very similar, and again, no obvious safety signal was identified.

We also looked at new medical conditions, compared the number and percent during the vaccination period through month seven and after month seven for selected organ systems and these percentages were comparable for the Gardasil and placebo groups in both time periods.

And the pregnancy outcomes summaries, this was, I believe, from the last safety update, but there was a comparable number of live births, spontaneous miscarriages and late fetal deaths in both groups.

The total number of congenital anomalies were similar in both groups, 15 in the Gardasil and 16 in placebo. One item of note was the number of infants with congenital anomalies that were born to mothers who received vaccine within 30 days of the estimated date of conception, in the Gardasil group 005, as compared to none in the placebo group. And these five infants had anomalies which were not apparently related, included hip dysplasia, ankyloglossia and pyloric stenosis, congenital hydroephrosis, club foot and congenital megacolon.

A similar pattern of an occurrence of SAE's were noted in pregnant women who were vaccinated with Gardasil and placebo, 4.2 percent in the Gardasil

group versus 4.3 percent in the placebo group and these events included conditions leading to c-section, premature labor and conditions generally associated with pregnancy.

There was a higher proportion of child with SAE's in women who received Gardasil while breast feeding in the vaccination period, 3.4 percent versus 1.8 percent, Gardasil to placebo and we just had made up a table and there was a difference in the numbers of respiratory infections that one saw with Gardasil and placebo. When you look at time course, though, after vaccination, these intervals ranged anywhere from 12 to 231 days after vaccination in the 17 infants in the Gardasil group and between three and 145 days in the placebo group. Again, the numbers are small, the time periods could be very long after vaccination. So it was unclear that we could make a strong conclusion. Just as a note, neither Gardasil nor anti-HPV antibody excretion in milk was specifically studied.

And the FDA safety conclusion is that although no obvious safety signal was identified, post-marketing pharmacovigilance activities will continue to collect adverse events that occur post-

vaccination in a larger population. And an imbalance was noted regarding the estimated date of conception of infants who had congenital anomalies, five versus one in Gardasil versus placebo. However, there did not appear to be a pattern among congenital anomalies. But as I'll note, they'll be a pregnancy registry that we'll be following subjects.

Immunogenicity, I just wanted to touch on this. The assay for the anti-HPV antibodies, it was noted that there was no immune correlative protection.

Bridging immune response from females 16 to 26 years of age to females nine to 15 years of age was important because females naive to the four vaccine HPV types are expected to benefit most from the vaccine and efficacy studies cannot be conducted in pre-adolescent girls.

This slide just shows month seven HPV 6 geometric mean titers by age of enrollment and we can see that on the left side of the slide, that's the younger age group and then as we go to -- down here, there's -- the age increases. So there's a higher immune response in the younger subjects. This pattern of decreasing immune responses with increasing age -- decreasing immune response with increasing age is seen

for other antigens as well.

Now, the immunogenicity bridging between the nine to 15 year old females was compared to the 16 to 26 year old females in the efficacy studies and we can see that the immune response in the nine to 15 year old females in protocol 016 and 018 were higher than those seen in the subjects who participated in the efficacy trial, and that was across -- for each HPV type in the vaccine.

Now, the duration of immune response, Dr. Barr has presented additional material, but we had, just to look at -- we had data for 18 out to 24 months and it shows that, again, we can see this is the people who were infected before and received placebo and these are the subjects that we see the vaccine who were naive before they received the vaccine. So you can see the anti-HPV 18 level increases by month seven and starts to drop off to this level by month 24, which is approximately the same level as those with natural infection. Again, we don't have the information past the month 24 time point.

This is the seropositivity rates for each anti-HPV 6, 11, 16 and 18 at month 24 for vaccinated women 18 to 26 years, with serology data at all time

points. And at 24 months, the seropositivity rates are all high at 96 to almost 100 percent, except for HPV 18 where the seropositivity rate was 74 percent.

Now, there was no obvious -- apparent breakthroughs of HPV cases at that point and it looked like from the figure, the GMT's had maintained at approximately the level, at least at month 24, close to what we've seen with natural infection. So that was noted.

Co-administration, just one slide. Gardasil with hepatitis B vaccine, the anti-HPV 6, 11, 16 and 18 immune responses were non-inferior when Gardasil was given with or without hepatitis B vaccine by seroconversion rates and GMT ratios and the anti-hepatitis B immune response was non-inferior when hepatitis B was given with or without Gardasil by seroconversion rates, although the anti-hepatitis B geometric mean titers were lower in the co-administration group at about 535 MIU's, as compared to those given -- when the hepatitis B vaccine was given alone at approximately 700.

The applicant's proposed post-marketing commitments include routine pharmacovigilance, phase IV studies and other studies.

The routine pharmacovigilance includes passive reporting of adverse events. The applicant has agreed to submit all non-serious adverse events to the FDA in monthly batches instead of quarterly and regular conference calls will be held between the sponsors, CDC and FDA, to better coordinate pharmacovigilance activities.

In addition, two phase IV studies are planned, an observational safety surveillance study and a large U.S. managed care organization that will investigate all serious adverse events within 60 days following vaccination and the Nordic long term follow-up study, which is a 10 year longitudinal evaluation of subjects in protocol 015 who are enrolled in Nordic countries. And this study, we use the national universal registries in four Nordic countries, mainly to evaluate vaccine and non-vaccine HPV related disease and HPV replacement, long term receptiveness and duration of immune response, potential safety signals and pregnancy outcomes.

Other studies will include those extensions of protocol 007 and 018 to evaluate long term effectiveness and duration of immune response and also to detect unanticipated safety signals through

active surveillance in all studies.

The FDA review conclusion, the safety, efficacy and bridging immune response data submitted to the BLA support licensure of Gardasil in females nine to 26 years of age, naive to the relevant HPV vaccine type for prevention of the following diseases or events: HPV 16 and 18 related cervical cancer, CIN 2/3 and AIS, HPV 6, 11, 16, 18 related VIN 2, VIN 3, VaIN 2, VaIN 3 and HPV 6, 11, 16, 18 related genital warts, VIN 1 and VaIN 1.

The applicants per protocol HPV type specific analyses that included a very high level of efficacy in naive subjects may not reflect the efficacy of Gardasil for all HPV related disease on a population basis. HPV related disease occurred in Gardasil recipients and some of these vaccine recipients were non-naive at baseline for one or more HPV vaccine types and some of these subjects developed HPV disease related to that HPV type with which they were infected. Subjects who were naive to all four vaccine HPV types could still develop disease related to an HPV type not included in the vaccine.

The modified intent to treat-3 population, again, we considered important because it included all

subjects across trials 005, 007, 013 and 015, demonstrate modest efficacy against CIN 2/3. For the types included in the vaccine, the efficacy was 39 percent with lower bound of 23.5 and across for any HPV type, the efficacy against -- overall efficacy for CIN 2/3 or worse was 12.2 percent.

Other concerns, longer term efficacy is of concern, but study 005, which is the one that has gone out the longest or has the longest amount of follow-up, at least for monovalent HPV 16 vaccine, suggests favorable longer term efficacy and the duration of immune response is also of importance.

I don't know if we want to go through the questions or not at this point, but we can stop here.

DR. FARLEY: Thank you, Dr. Miller. I think we can, at this point, I would prefer to use the time, rather than going through the questions again, to allow questioning from the panel, and we can go a little bit over. We've allowed an hour and a half for lunch and probably don't need that much time. So maybe we can spend the next 15 or more minutes questioning, if there are questions from the group.

Let's start with Dr. Maldonado.

DR. MALDONADO: One of the obvious

differences between the sponsor and FDA is the issue of male and female infections. This is dog-tied -- looks pretty convincing that this vaccine is -- also prevents the infection. Do you have any biological plausibility that the vaccine will not be efficacious or safe in males.

DR. MILLER: Well, again, we have no efficacy data right now in males and we -- that's a point. I know there's been -- just an article with HSV vaccine that there was efficacy in women and none were noted in males. It's just one study.

We also know that the efficacy study is ongoing at this point and an extension to males will be considered when we have that data available. We don't really have any safety data in males right now over the age of 16 -- or over the age of 15 and I guess a predominant amount of efficacy was seen in cervical lesions and vulvar and vaginal lesions.

DR. FARLEY: Dr. Royal.

DR. ROYAL: I have a question about slide 39. Going back to the increased frequency of cases and immunized individuals who are PCR positive and serologically positive compared to the placebo group.

DR. MILLER: Okay.

DR. ROYAL: Whether or not -- is there anything known about the antigen specificity of the antibodies produced and whether some might be associated with an increased risk of developing disease?

And also, in the group that's PCR negative and seronegative, going back to how the PCR is done, it's done on paraffin-embedded tissue, which is essentially cooked and you wonder if maybe that's a false negative and perhaps, with a more sensitive test, that person would be in a PCR positive, seronegative group, which actually does develop cases and in thinking about understanding the true risk for individuals in the various groups going on to develop disease, you'd want to be sure about that.

DR. MILLER: Well, regarding -- I'm really not sure about the antibody question. I'm not -- I really don't have any real hard data to say what biological plausible explanation could be present for that.

As far as the assay is concerned, I might ask one of my colleagues just to speak about the assay, but when you looked at the data sets, just there were -- you could see that people were infected,

you know, with the HPV 16 in the beginning and they got Gardasil and they might have gone on to develop that particular disease. There were also, in the placebo group likewise, there were negative -- there was no evidence of infection by their initial status of PCR testing or seropositivity and they did the -- I mean, there was more, definitely, in that particular group. You saw an imbalance in a positive way for placebo versus Gardasil.

DR. ROYAL: It's just interesting, in the lowest risk group, you are seeing a case and a false negative test could explain that. It's only one case, but again, it's a matter of understanding the true risk.

And my first question goes to the point of whether or not it's advisable to immunize individuals who are dually positive by PCR's and by serologic testing?

DR. MILLER: I don't know if that's widely available at this point. But I don't believe screening was entertained as part of, you know, when this vaccine was in use, but it's something that we were concerned about and we're -- I think to be followed, I think the long term pharmacovigilance

studies will help determine if there's any, you know, PCR -- what the status is as time goes on, especially in the carefully controlled -- the carefully monitored Nordic countries.

DR. FARLEY: Dr. Greene.

DR. GREENE: With respect to that same issue, I had a question. In the materials that were distributed to us prior to the meeting, in the FDA's background document, table 18, was an analysis of the study 013, selected characteristics for sub-group of PCR positive and seropositive. And it sites what appears to be some imbalance between the groups, between the Gardasil and placebo, with respect to factors that could pre-dispose to a risk for CIN 1, 2 and 3. It seemed to me that that could easily be addressed with a formal regression analysis of that data, but I didn't see one and I was just wondering whether the agency had done a formal regression analysis to take into consideration, those risk factors?

DR. MILLER: I don't believe -- Henry, is a formal analysis done? I don't think so.

DR. HSU: Henry Hsu. The question you just addressed about the regression analysis, yes, we did

thought about that, but we thought it will be too much exploratory in the first place. Then the second is that the data we actually have and we're just not sure that we are going to extract the correct data.

In addition, we actually thought about the, kind of the covariance type of the adjustment, but we did not try that.

DR. FARLEY: Can I ask a question about the, I think it's slide 42, which was looking at the CIN 2 and 3, that it was non-vaccine related and whether there were any trends in -- I guess the question, at least hypothetically or the concern would be, replacement if we eliminate 16 and 18, will it be replaced and were there differences under immunologic pressure between those cases, those who had been immunized, had -- is that -- 42, I think, is the -- let's see --

DR. MILLER: Right, that's due to any type. I'm so sorry. There it is.

DR. FARLEY: So the 36 cases in the immunized versus the 27 cases in placebo, were there differences in which types of HPV they were infected with?

DR. MILLER: I'm not aware of differences.

I know that we -- they did not test for the non-vaccine HPV types, so I don't believe -- I don't have that information about which other types they might have been infected with.

DR. FARLEY: So that's actually unknown information, since you weren't testing for those beyond the four?

DR. BARR: This particular analysis is an analysis that we feel is biased against the vaccine because it's an all MITT-1. It excludes risk in a differential way between vaccine and placebo, in that -- and we have data that shows that if you look at the excluded people in this population, the people in the placebo group who are excluded -- I'm sorry, the people that -- excluded in the placebo group were high risk people, most likely to get disease.

And so what we see is that there is a strong differential risk bias here that goes against the vaccine. We have looked at replacement formally using analyses that look right from day one and we see no replacement, not for infection in protocol 5 and not for disease not caused by vaccine HPV types in protocol 13 and 15.

So I think it's really important to

understand that this particular analysis has a risk bias against the vaccine.

DR. FARLEY: Dr. Emerson, please.

DR. EMERSON: The bias that creeps into this is what I -- again, so I can understand that if, in your definition of what is a cause is just because you can see hepatitis -- I'm sorry, you can see the HPV 16 there, that makes you declare something is the cause. And so by that same token, if I gave a vaccine for chicken pox and I was looking at renal failure, I could say that if I had an efficacious vaccine against chicken pox, that all the renal failure was not caused by it, even though I didn't affect the renal failure.

Now, in this same idea, we can be having some CIN 2/3 that was going to be happening anyway and that the error was we were attributing it to 16.

DR. BARR: Or the bias is -- if I can be allowed to show a slide, I can show what the bias is. But there is a bias. It takes -- because the risk of disease is strongly correlated with sexual behavior and other parameters. This is a well known feature of HPV infection disease. The correlation between 16 detection and the lesion and the presence of that lesion is a well evaluated and accepted tenet of the

field. It's not varicella and renal failure, for example, as you -- to use your example, that HPV 16 is there, it is the causal type. That is -- there's a huge body of data that has looked at these particular kinds of assays and the correlations between them and the risk for disease.

If I may though, the biggest problem with this analysis right here is the bias in risk, because if you can imagine, imagine if you included women who had lots of sexual activity in one arm, just to extrapolate this, and virgins in the other arm. You can imagine that you can create efficacy for the vaccine or for the placebo, depending on what the sexual behavior patterns are in the two arms. That's not right.

What's happening here is that you're specifically excluding individuals who become infected with a vaccine HPV type from the analysis of the placebo group versus the vaccine group and hence, when you're looking at non-vaccine type infection, you're taking the people who are particularly at risk for HPV and excluding them from the placebo group, but not from the vaccine group.

So the difference here is that they

started to count at month seven, okay. They are starting to count here at month seven so that the period of risk -- if I can just show a slide, I can really explain this a little bit better.

DR. EMERSON: Probably that might be better after lunch.

DR. BARR: Not a problem. But I can assure you that what's happening here is then in the first seven months of follow-up, what they're doing is they're excluding people who are infected with any HPV of the four types during the first seven months. And so if you think about it, the vaccine is efficacious starting from day one. We already between day one and month seven that the vaccine is highly efficacious. And so what's happening is, is the infected people in the placebo group who get kicked out, there is people in the vaccine group who aren't infected who get to stay in, the people that get -- and then you're looking at non-type after month seven.

So what's happening is, the people that get kicked out between day one and month seven have like a two or three times higher risk of chlamydia, twice as much sexual activity behavior and they're being included in the vaccine group because they

didn't get infected, but they can be excluded from the placebo group by the fact that they get infected and there's 564 in the placebo group and only 100 people that get excluded in the Gardasil group. There is an imbalance of exclusion. There's an imbalance of risk, and that's why you see this imbalance in numbers.

DR. EMERSON: Okay, but that's exactly the point that I think we're trying to make here, is that that very exclusion process is coming from the fact that you are attributing presence of 16 or 18 as proof of causation and that's what's open to question, is whether all the CIN 2/3 that we see, with 16 or 18 present, is in fact caused by that 16/18 or whether there was some sort of permissive sort of growth of the 16/18. I don't believe that the experiment has been done to prove that every time that you attribute the 16 is definitely due to that cause, that your assays can prove that. I don't think it would be ethical.

DR. KOUTSKY: Laura Koutsky from the University of Washington. And I think the point that's important to make is, that I've heard said by Dr. Peter Howley, we probably know more about the way HPV 16 and 18 cause cervical cancer than we know about how other

agents cause other cancers, and it has to do with the E6 and E7 proteins that are produced by HPV high risk types, particularly HPV 16 and 18, and that when there is a high risk lesion or a high-grade lesion, such as CIN 3, what has happened essentially is the virus has infected an immature cell that is prone to replicating and in some fashion, that E6 and E7 has gotten expressed to high levels and it has allowed those cells to accumulate, essentially in a mortalized clone of cells, that you can imagine over time that does not have the normal breaks to say stop replicating, clean up your DNA or die. It's the -- E6 and E7 are efficient in allowing that cell to continue to replicate with the DNA damage. And that over time, the 15 to 20 years on average, leads to an invasive cancer clone.

So I think it's not -- it's clear that HPV 16 and 18 do cause these pre-cancerous lesions and they do cause the cancers.

DR. FARLEY: Do we have additional questions?

DR. GREENE: One other question.

DR. FARLEY: Dr. Greene.

DR. GREENE: Since by analogy, you just

happen to just mention varicella, there was a registry, pregnancy registry, for the varicella vaccine, which eventually, after some reasonable period of time and large numbers of exposures with no evidence of a safety signal, was eventually shut down. Is the -- has the agency thought about any kind of a sunset or how long are these post-marketing surveillance commitments anticipated to run?

DR. MILLER: I'm going to ask Dr. Izurieta just to comment on that.

DR. IZURIETA: We are of course, still negotiating these and any input from you will be very, very welcome in this negotiation. But probably the most important of these would be the Nordic cancer, registry studies that are two parts to that proposal and I will ask the sponsors to correct me when and if I'm wrong.

There are four Nordic countries which have a cancer registry which will be active after licensure. Those are Norway, Denmark, Iceland and Sweden. That is proposed right now to be followed up for 10 years, but there are negotiations to extend that for probably up to 14 years.

The other thing is, these are women which

are approximately 5,400 and a little more, women from the protocol 15. Their agreement, and correct me again, if I'm wrong, the agreement with these persons is that they can be followed up for life if and when necessary.

So there is a potential for cancer outcomes and other disease outcomes in these countries which have a highly sophisticated system of registries for morbidity, for mortality, for birth and for other things, to be followed up for us as needed.

The other very interesting aspect of this is that Norway, the Norway project, as it was presented today, Norway has accepted to start an HPV vaccination registry which will be universal and we know that in general, Nordic countries have a good record of keeping universal registries and we have seen very sophisticated studies from them. So there are reasons to trust that this will happen that way.

Now, on the other hand, they will also have birth -- they do already have a birth registry and their -- again, correct me if I'm wrong, but you can match the birth registries and the outcomes of pregnancy with the HPV registries, basically doing an observation of, hopefully, universal, nationwide or

similar study, comparing the outcomes of pregnancy with the vaccination status and have some kind of observational study results, which we compare vaccinated outcomes of pregnancy among vaccinated women with outcomes of pregnancy among non-vaccinated women.

Also, probably some other of the Nordic countries could enter into similar registries, but for that, we do not have any commitment. And again, any input from you will help us improve these negotiations and get what we think is correct and the sponsors have, report to -- indicated that they will be willing to negotiate post-licensure agreements.

MS. DANA: Hello, I'm Adrian Dana and I'm from the Clinical Risk Management and Safety Surveillance Group at Merck and I wanted to just make a couple of clarifications, if I could. One is that Merck does currently maintain the varicella pregnancy registry and we are currently in the process of analyzing year 11 of that pregnancy registry, so that remains active.

And I did want to just make one other little clarification. We do plan to do a pregnancy registry similar to the varivax pregnancy registry,

which is based on spontaneous reporting and that registry is distinct and in addition to the Nordic cancer registry studies, which will also look at pregnancy in that population, and in addition to the post-marketing safety surveillance study, which will look at the descriptive epidemiology of pregnancy exposures.

DR. FARLEY: Thank you. Any other questions for the morning session? If not -- one question?

MS. KRIVACIC: I have one regarding the Nordic study and that is in terms of when we can find out if there is some kind of effect with the patient population, regarding cervical cancer, will there be, I guess, enough of a power at say, five years or 10 years for that population to actually be looked at, or how long until we can see some kind of efficacy regarding cancer prevention? I guess what I'm trying to say is the age range is now what, 19 to 26, in that group?

DR. FARLEY: Let me just interject that that was a question from Susan Krivacic, who is our patient representative.

MS. LUPINACCI: I'm Lisa Lupinacci from the Biostatistics Group at Merck. We intend to follow that

cohort through 10 years and we have approximately 90 percent power, if our vaccine efficacy drops to about 75 percent relative to what we're seeing now, to detect that by year seven or eight in the study.

MS. KRIVACIC: Will you compare it against a placebo group at all?

MS. LUPINACCI: We are going to look at a couple of different aspects. One thing that we're going to look at is the cumulative vaccine efficacy and we're going to evaluate that in the context of a conservative placebo rate, based on, obviously, there won't be any placebo people in the extension because we'll have to vaccinate the placebo subjects in protocol 15 at the end of that study. Everyone then in the follow-up period be on the Gardasil -- will have received Gardasil.

However, we will be using the placebo data at the end of protocol 15 to help us evaluate the rates that we see of cumulative cases during the study. We also have a plan to evaluate annually any clustering of cases that we see, because we think that's an important feature of this as well.

DR. FARLEY: One more question, Dr. Markowitz.

DR. MARKOWITZ: Actually, I have two questions. In the Nordic cancer extension, is there going to be antibody titers followed as well?

DR. BARR: The answer is yes, at year five and year 10.

DR. MARKOWITZ: I just wanted to say that I still don't understand that slide 42 that was up there and what the bias was that was introduced. So I would like some more clarification.

DR. FARLEY: Well, I would suggest that maybe you can spend your time at lunch and sort of come up with the best way to help us understand it and then maybe they can do that in the beginning of our discussion session after the open public hearing.

Okay. Very good. Well, let's break for lunch. We want to regroup at 1:30 and we'll start with the open public hearing at that time.

(Whereupon, the foregoing matter recessed at approximately 12:15 p.m.)

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

DR. FARLEY: Thank you. Welcome back to this VRBPAC meeting session for the afternoon. I'm going to start the afternoon session by letting you know that we have a number of FDA representatives who

have joined us at the table up here for discussion purposes only. They are not going to be voting members, but they are here to facilitate the discussion that we anticipate this afternoon. And I'm going to have them briefly introduce themselves to start out with.

DR. GOLDENTHAL: I'm Karen Goldenthal, Director, Division of Vaccine Applications.

DR. MILLER: I am Nancy Miller. I'm Medical Officer.

DR. TOERNER: I'm Joe Toerner. I'm Medical Officer.

DR. FARLEY: Thank you. We're going to proceed to the open public hearing and to start that out, we have a couple of statements that are required for us to read and I'm going to first turn it over to Christine Walsh.

MS. WALSH: Thank you, Dr. Farley. As part of the FDA Advisory Committee meeting procedure, we are required to hold an open public hearing for those members of the public who are not on the agenda and would like to make a statement concerning matters pending before the Committee.

Dr. Farley, will you please read the open

public hearing statement?

DR. FARLEY: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with a sponsor, its products and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Thank you. Christine.

MS. WALSH: I have received five written statements. Copies have been placed in the Committee member's folders, the viewing notebook at the registration desk and will be made part of the official meeting record.

I have also received 10 requests to speak today. I will be introducing everyone to speak and one speaker did ask not to speak, so your order -- the order that I call you in might be a little bit different.

Also, for the speakers, just to note, that if you'll notice in front of the room near the podium, we do have a timer. At the end of the time you're allotted, it will flash red, so please, if you could, just stay within your time limit for speaking.

Our first speaker is Dr. Bobby Gostout, representing the Society of Gynecologic Oncologists. Dr. Gostout.

DR. GOSTOUT: And thank you for the opportunity to present on behalf of the Society of Gynecologic Oncologists.

I am an Associate Professor of Gynecologic Oncology at the Mayo Clinic in Rochester, Minnesota and as you said, representing the Society of Gynecologic

Oncologists today. And by way of disclaimers, the Society has received educational grants from Merck to support the annual meeting on women's cancers. We do not receive any specific support from the Vaccine Division and my travel has been paid for by the Society of Gynecologic Oncologists.

I'm here today to represent the physicians who treat women for whom prevention has failed. Gynecologic oncologists are obstetrician-gynecologists with an additional three to four years of training. We're trained in the comprehensive management of patients with female reproductive cancers, including both surgery and the administration of chemotherapy.

Almost all practicing gynecologic oncologists are members of the Society of Gynecologic Oncologists.

It is especially important that you hear our perspective, because you have an opportunity today to approve a vaccine that can reduce the incidents of cervical cancer and precursor lesions. Not since the introduction of the Papanicolaou test over a half century ago, has such an opportunity to make a real difference existed.

Since the introduction of the Pap test,

the incidents of cervical cancer in the United States has been dramatically reduced and the death rate has declined by 74 percent. Despite this important advance, however, each year over 10,000 women are diagnosed with invasive cervical cancer and 3,700 women will die from a potentially preventable disease in 2006.

Let me put a human face on these statistics. This cancer disproportionately affects women during their child-bearing years and child-rearing years, resulting in child-less couples and for women who have late diagnosis, leaving behind mother-less children.

I see these women in my practice. One patient, Cheryl, particularly exemplifies the human cost of this disease. After years of normal Pap tests, she was diagnosed with an invasive cervical cancer six months following the birth of her second child. She endured an initial surgery to diagnose the cause of her abnormal bleeding, a second surgery to treat her cancer and she required subsequent radiation therapy. Because of these procedures, she was away from her children for about eight months, more than she was with them. With what we knew about her disease, the odds were against

her surviving this cancer.

Over the next five years, her eyes met mine in fear many times when a symptom or physical examination finding gave us reason to worry that the cancer was back. With each scare, I saw a plea in her eyes. I understood what she was telling me. She was telling me with her eyes, "I can't die now. My young family needs me."

It is now more than five years from her treatment and we're feeling confident that Cheryl will survive. Unfortunately, I could also tell you similar tales of patients who did not.

I caution you to not console yourself by telling yourself quietly that this cancer doesn't happen to women like you or your family members. I assure that many of the patients I see could easily be your sisters, cousins, aunts or nieces. This cancer affects real women, women like you, your family members and women like me.

I caution you not to tell yourself that prevention through screening has worked. I'd like to bring to you the number of women that I see who have invasive cervix cancer in spite of complying with screening exams. And I caution you to not believe that

you can apply the vaccine only to women who perceive that they are at risk, because I tell you every woman that I see with cervix cancer looks at me with shock and did not understand that she was at risk.

What is so heart-wrenching for me to treat women like Cheryl is the knowledge that we're close to being able to eliminate this cancer. SGO urges you to take the next step in this quest today by approving the broadest possible application of the vaccine in order to afford the maximum protection to as many women as possible, as early as possible.

On behalf of the Society, I thank you for the opportunity to provide this statement. In your copy, you have a copy of the statement from the Society of Gynecologic Oncologists, our position statement on the vaccine. Thank you.

MS. WALSH: Thank you, Dr. Gostout. Our next speaker is Susan E. Holleran, representing the Coalition of Labor Union Women. Ms. Holleran?

MS. HOLLERAN; First, we've gotten no money from Merck and I'm here as a volunteer, so there's been no money involved.

Good afternoon. My name is Susan Holleran. I'm am D.C. Alternate State Vice President

of the Coalition of Labor Union Women. CLUW is the only national organization of union women in the United States. Through the various communication channels available to us, CLUW reaches out to the 6.5 million union women across the country.

Founded in 1974, CLUW has long been committed to promoting women's health. The labor movement has always recognized the significance of preventive health care and with the current health care financial crisis, we believe that prevention is more important than ever.

In addition to our primary concern to alleviate human suffering, we know that catching illnesses early can provide huge savings to our nation's health care costs.

When we learned that the HPV virus causes cervical cancer and that with the right tools used on the right women, we can eliminate this disease. CLUW made cervical cancer prevention a priority issue. In 2003, CLUW urged the FDA to approve the HPV DNA test for women over 30. In 2004, CLUW was part of the Centers for Disease Control and Prevention funded project, Working Women ROCC, Reaching Out Against Cervical Cancer.

This project's goal was to raise awareness of cervical cancer and it's potential elimination with a primary focus on union women at highest risk, those in under served populations. In early 2004, CLUW created its own cervical cancer awareness program, Cervical Cancer Prevention Works, which is funded by an educational grant from Digene, the company that manufactures the HPV test.

As a result of our efforts, we know that hundreds of thousands of union women have heard our message and taken action and that even more have insurance coverage for the HPV test in addition to the Pap.

CLUW is pleased that girls and young women can help protect themselves with the new HPV vaccine. However, since the vaccine targets just two of more than a dozen types of HPV that can cause cervical cancer, protection will not be complete unless women are also screened regularly once they become sexually active.

For women who are already sexually active and thus probably exposed to the targeted types of HPV, the data available today do not indicate any substantial benefit from the vaccine. Therefore for

the vast majority of women today and for many in the future, regular screening is their primary weapon against this disease.

CLUW believes that any communication about cervical cancer to women and to their health care providers needs to emphasize the importance of ongoing screening.

Today, the growing body of data is compelling in its demonstration that the most effective screening protocol is use of the Pap in women under the age of 30 and the combination of Pap and HPV tests for those over 30.

CLUW joins in the excitement created by the significant potential benefit of this new vaccine. However, we call on you today to keep the big picture in mind. We ask the vaccine manufacturers and other interested parties to include education on the need for ongoing screening and all communication related to the proper use of vaccination and to join us in educating women and health care providers on the most effective screening options available to them today. Thank you.

MS. WALSH: Thank you, Ms. Holleran. Our next speaker is Dr. Beth Jordan, representing the Association of Reproductive Health Professionals. Dr.

Jordan.

DR. JORDAN: I have no personal financial relationship to disclose.

My name is Dr. Beth Jordan. I'm Medical Director of the Association of Reproductive Health Professionals, ARHP. ARHP was founded in 1963 and is a multi-disciplinary professional association with over 12,000 coordinate associate members, including physicians, advance practice clinicians, researchers and educators, all with expertise in reproductive health, research or practice.

ARHP and its members provide reproductive health services or education or conduct reproductive health research. ARHP fosters research and advocacy to improve reproductive health.

ARHP advocates for evidence based research and supports the availability of an education about a wide range of safe, effective and appropriate new technologies to enhance the health of all women.

On behalf of ARHP and its members, I am honored to provide comments before this Advisory Committee in support of the approval of the HPV recombinant vaccine. Our support is based on the following:

There are very few medically proven mechanisms to prevent cancer. The HPV vaccine represents a rare opportunity to prevent cervical cancer, which affects over 15,000 women in the U.S. each year. The research demonstrates that this vaccine is both safe and effective in preventing the infection with the most dangerous strains of the cancer causing HPV.

The vaccine, along with appropriate screening, including Pap tests and DNA tests, are important measures towards the eventual eradication of cervical cancer, through a combined approach, prevention and early detection.

In order to ensure the most appropriate and effective use of this product, public and provider education will be needed.

For these reasons, ARHP respectfully recommends that the FDA move forward with the approval process for the HPV vaccine. Once approved, ARHP is committed to providing the necessary education surrounding this vaccine to health care providers, patients and parents.

I would like to thank the Committee for the opportunity to present this statement of support on

this important public health issue.

MS. WALSH: Thank you, Dr. Jordan. Our next speaker is Mr. Sean Tipton, representing the American Society for Reproductive Medicine. Mr. Tipton.

MR. TIPTON: Thank you very much. The ASRM has only a commercial relationship with other divisions of Merck, that is, they buy ads in our journal.

The American Society for Reproductive Medicine is a medical professional society with close to 8,000 members committed to promoting the reproductive health of women and men through research, professional and patient education and advocacy and health care policy. We appreciate the opportunity to provide our views on this important matter today. In a nut shell, we urge your approval of this vaccine, which we think will eventually lead to a significant decrease in the incidence of HPV in the United States.

As you know, the virus is transmitted through skin-to-skin contact and even though condoms do provide protection, they do not adequately protect against all HPV transmission since they don't cover the entire affected epidermis completely.

So while the risk of HPV infection can be

greatly minimized through behavioral controls, sexual abstinence forever is not practical for most people and maintaining a monogamous relationship is no guarantee that your faithful partner has not previously contracted a persisting HPV infection.

We believe the vaccine should also be made available to men, because even though the effects of HPV infection in men are less well quantified, oncogenic HPV has been implicated in anal cancer and cancer of the penis. In addition, male vaccination would reduce the incidence of infection for HPV 16 and 18 in the portion of the female population that might remain unvaccinated.

We urge the Committee to approve the vaccine in the hope that its widespread administration of the vaccine of America's women will be safeguarded in the future from deadly cervical cancer. Thank you.

MS. WALSH: Thank you, Mr. Tipton. Our next speaker is Ms. Martha Nolan, representing the Society for Women's Health Research. Ms. Nolan.

MS. NOLAN: For disclosure, the Society does receive unrestricted educational grants to support our programs from Merck, but in no way received any money related to this vaccine or this hearing.

My name is Martha Nolan and I'm the Vice President of Public Policy for the Society for Women's Health Research, as the nation's only non-profit organization whose mission is to improve the health of all women through research, education and advocacy.

The Society considers the availability of a potential vaccine to prevent the human papillomavirus that causes cervical cancer, an incredible breakthrough that has the ability to spare thousands of women the fear of cervical cancer and the suffering associated with it.

The Society strongly urges an expedient review and decision and depending on positive efficacy safety concerns, approval to allow this break-through advance to be available to women as soon as possible.

Cervical cancer is a serious health threat for American women and prevention efforts are critically important. As the FDA reviews the new HPV vaccine and a second vaccine review expected later this year, it has the opportunity to eradicate this terrible disease and move toward a world without cervical cancer. Both vaccines have shown great promise in clinical trials, providing 99 percent protection from HPV infection.

We want serious consideration of the research and evidence as these vaccines have the potential to dramatically reduce the incidence of cervical cancer, dysplasia and the cost of the medical community to treating these conditions.

In addition, the Society would encourage good phase IV clinical studies be implemented upon approval of these vaccines to monitor their widespread use in the population.

The ability to successfully prevent HPV infection would have tremendous impact on the lives of women and men, but particularly young women.

Currently, women live in fear of contracting HPV. These vaccines could eliminate this threat and deadly cancer within our life times.

The Society for Women's Health Research encourages the FDA to seriously consider the research in evidence for these two HPV vaccines as quickly as possible, as women's lives are at stake. The Society would recommend that there be research in vaccine development in all areas to improve the lives of women and men.

We appreciate your efforts to improve the health of American women and prevent unnecessary

suffering and early death due to cervical cancer. Thank you for the opportunity to speak today.

MS. WALSH: Thank you, Ms. Nolan. Our next speaker is Ms. Kathryn Guccione, representing Women in Government. Ms. Guccione.

MS. GUCCIONE: Thank you. Women in Government does receive unrestricted educational grants from Merck.

My name is Kathryn Guccione. I'm the Senior Public Policy Associate at Women in Government. Women in Government is a national 501(c)(3) not for profit, bipartisan organization of women state legislators, providing leadership opportunities, networking, expert forums and educational resources to address and resolve complex public policy issues.

As you all know, cervical cancer is preventable. We know what causes it, the human papillomavirus. Women in Government believe that the availability of a vaccine for HPV will be a critical step toward eradicating this disease.

In 2004, we created the Challenge to Eliminate Cervical Cancer Campaign, which mobilizes state legislators to improve education and awareness about HPV and cervical cancer and to help ensure that

all women have access to the best available screening and preventive technologies, regardless of their socioeconomic status.

This campaign has garnered support in 45 states to date, of which 39 have enacted legislation or resolutions aimed at cervical cancer prevention.

Women in Government pledges to continue our outreach to the states on this important issue, now adding available and important information about HPV vaccines, plus state policy makers will play a vital role in the adoption and success of implementation of this vaccine and each be educated and informed.

Women in Government strongly believes in access to health care services for all. We encourage the FDA to help ensure that life-saving vaccines are available to all for whom they are indicated.

Women in Government believes that an FDA approved HPV vaccine would be part of a comprehensive strategy to eliminate cervical cancer. We believe it is important that this strategy also includes screening for cervical cancer, using advanced and appropriate technologies to target those HPV types that are not covered by the HPV vaccine currently under review.

Continuing to develop programs to reach

all women, incorporating new preventative technologies, such as an HPV vaccine, is essential to our collective goals. By ensuring access to advance and appropriate preventative technologies, we can truly eliminate cervical cancer.

I thank you for the opportunity to participate in this meeting today and look forward to your decision on this important public health issue. Thank you.

MS. WALSH: Thank you, Ms. Guccione. Our next speaker is Ms. Amy Allina, representing the National Women's Health Network. Ms. Allina.

MS. ALLINA: Thank you. The National Women's Health Network is a non-profit organization that works to improve women's health by influencing policy and supporting informed consumer decision making in health care. And we accept no financial support from any pharmaceutical companies, medical device manufacturers or other companies that have a financial stake in women's health care decision making.

You've already heard a number of speakers say, we agree that the HPV vaccine holds the potential to make a very important contribution to women's health and based on the data presented by Merck, this vaccine

appears to be safe for use and highly effective when given prior to exposure to HPV. So we just want to say today that we do support approval of this product and we want to make three brief points regarding the vaccine.

The first is that the follow-up research with the study population and additional post-approval research are very important so that we can learn more about the safety and efficacy in the general population and real world use, as well as longer term efficacy. So it's critical that those efforts will be continued.

The second point is that the potential value of this vaccine is particularly significant for women who are most vulnerable to cervical cancer and many of those women don't have access to health care services. So we're urging -- we're using this opportunity to urge the company, in particular, to support programs that will ensure access to the vaccine for those women.

And then finally, we want to make the point that we'd like to see the FDA mandate some kind of labeling or other mechanism for communicating to health care providers and patients the necessity of continued regular screening for cervical cancer. Thank

you.

MS. WALSH: Thank you, Ms. Allina. Our next speaker is Ms. Ellen Stovall, representing the National Coalition for Cancer Survivorship. Ms. Stovall.

MS. STOVALL: Good afternoon. I'm Ellen Stovall, President and CEO of the National Coalition for Cancer Survivorship. We're a non-profit organization celebrating 20 years advocating for quality cancer care for all Americans diagnosed with or who are at risk for cancer.

I myself am a 35 year two time survivor of Hodgkin's lymphoma and by way of disclosure, my organization has received unrestricted grant funds from Merck's Oncology Unit, but no funding from their Vaccine Division.

Over the last 15 years, we've enjoyed the long time collaboration with your colleagues at FDA, particularly in the Center for Drugs, who review and approve cancer therapies for people who already have cancer and we have actively participated in FDA programs that train cancer survivor advocates and utilize their expertise to inform the process of reviewing new cancer therapies.

It's our distinct pleasure to be here for the first time and to comment on the impressive performance of a truly preventive intervention against a group of cancers that cause a good deal of pain and suffering for those who are affected.

Despite an extensive effort at screening, which we certainly agree should continue for the indefinite future, many women, around 10,000 a year in this country alone, find themselves with the diagnosis of cervical cancer. Another roughly 6,000 women will be diagnosed with vaginal or vulvar cancers, that may even be more difficult to detect at an early stage and carry many morbidities associated with multi-modality treatments for these cancers that can impair fertility, sexuality, continence and overall quality of life.

Because these cancers are caused by sexual contact and resulting viral transmission, they may create more of a sense of isolation and stigma for those who are diagnosed with them. That may be one reason why this Committee has not received more requests for appearances by cervical cancer survivors. Their absence certainly does not reflect a lack of suffering associated with this terrible disease.

In light of the very impressive clinical

trial results reported here today, we urge the FDA and this Committee to make the vaccine available to the widest possible population supported by the data, including evidence based on antibody comparisons, if appropriate.

If widely used, this vaccine can prevent thousands of cervical, vaginal and vulvar cancers, as well as many anal and penile cancers and head and neck. Aside from its value in preventing the human suffering and financial costs associated with these cancers, the vaccine will provide an inspiration to researchers to redouble their efforts to finding a meaningful prevention strategy for cancer through vaccines or otherwise. Thank you for the opportunity to make comments.

MS. WALSH: Thank you, Ms. Stovall. Is there anyone else in the room who would like to address the Committee at this time? Please identify yourself.

MS. ARRINDELL: Deborah Arrindell, American Social Health Association. Good afternoon. I thank you for the opportunity to make a statement on behalf of the American Social Health Association. Our organization has, in the past, received unrestricted

educational grants from Merck.

Our organization has been fighting to eliminate sexually transmitted diseases and their harmful effects on communities and families since 1914, about 92 years, a fact that my 20 year old son finds amusing and not worth describing. Ninety-two years and we haven't gotten there quite yet.

We've had an HPV and cervical cancer resource center since 1998 and through that center, we talk to thousands of people each year. We operate a live chat room every day, talking to people with HPV and cervical cancer. And in addition to that, this year we will probably answer over 4,000 e-mails about HPV and cervical cancer.

In short, we talk to a lot of people about this disease, this infection, and we understand first hand the real complexity of communicating about HPV and cervical cancer. Research, as you know, shows that both patients and providers find this a very difficult and complex and challenging disease with its variable clinical presentations to understand and talk about.

So we believe that targeted provider and public education efforts will be essential and to the extent that that's within the jurisdiction of this

Committee to make happen, we hope that you will encourage that.

Most importantly, we believe that it is essential for consumers to be aware that even with immunization, comprehensive cervical cancer screening, as you've heard from many of our colleagues today, will be essential and must be continued.

We would urge the FDA, then, to require that the package insert direct health care providers administering the vaccine to advise all female patients and parents of children of the importance of routine cervical cancer screening and appropriate follow-up.

As this Committee knows, continued screening will be especially important for detecting the remaining 30 percent of cancers from high risk HPV types that are not included in the vaccine. Additionally, we know that the vaccine doesn't protect against previous infection and whether the vaccine provides multi-decade protection or if efficacy will decrease after five years is something that we don't know yet.

Finally, although it's outside the jurisdiction of this Committee, we would really urge you, as our colleague did before us, to be aware of the

importance of ensuring access for low risk -- for high risk, low income populations. The Department of Health and Human Services has noted that cervical cancer rates are actually sentinel markers for other kinds of serious health issues and concerns in communities that are systemic issues and that must be handled by other programs, cancer control programs in addition.

These access issues that are currently problematic in these populations will not be alleviated by simply the development or approval of a vaccine. Access for those groups who bear the highest burden of cervical cancer must be a public health priority. Population protection has proven very effective in addressing these racial disparities.

We are very excited about the prospect of this rapid approval and availability of this vaccine. The American Social Health Association will do everything within our resource limitations to support widespread availability and acceptability of these vaccines.

We appreciate FDA's commitment to providing accurate information regarding the benefits and limitations of the products that it approves. Thank you.

MS. WALSH: Thank you. Is there anyone else in the room who would like to address the Committee?

(No verbal response)

MS. WALSH: Okay. We'd like to thank everyone who has made a statement today. Dr. Farley, I'll turn the meeting back over to you.

DR. FARLEY: Thank you, Christine. At this point, we're going to start the process of discussion of the vaccine, but to begin this process, we'd like to go ahead and give Merck, the sponsor's representatives, the opportunity to follow up on the conversations started at the morning session about slide number 42 and related issues and we'll lead then into the presentation of the questions, followed by opportunity for further discussions.

DR. BARR: Thank you very much. I'm Eliav Barr, head of the clinical program for Gardasil. I wanted to discuss what we have done to evaluate replacement, which is the issue that's being addressed -- that's attempted to be addressed in that slide, 42. We also want to explain why we believe that that analysis is confounded. Can I have slide 454, please?

Okay. This -- I wanted to describe the

population that's being reviewed here. These are women who are naive to all four vaccine HPV types at day one. They remain naive to all four HPV types through month seven and then we start counting after month seven.

The analysis underestimates vaccine impact in two ways, one which isn't confounded and one which is confounded. The one that's not confounded is that it includes cases caused by non-vaccine HPV infection present at day one and similar numbers of cases should be added to vaccine and placebo group. This is not an issue for our concern about this analysis.

What we are concerned about is that the analysis conditions introduce differences in risk of HPV infection between vaccination groups. Specifically, there is a preferential removal of two kinds of populations that are at risk for HPV infection from the placebo group, but not from the vaccine group, women who engage in high risk behavior and women who are at intrinsically higher risk of HPV infection, evident by the fact that they already have an infection.

Next slide, please, 455. Okay. Now, just as a point of reference, subjects who engage in high risk behavior are more likely to be infected with

vaccine HPV types and non-vaccine HPV types than the rest of the population. Sexual activity and differences in numbers of sexual partners represents the most powerful predictor of risk for infection with HPV.

Gardasil is already efficacious during the vaccination period. We have efficacy above 90 percent for infections that start right after day one. So placebo subjects, but not vaccine subjects, acquire infections. These high risk subjects are removed from the placebo group by the analysis condition, but not from the vaccine group, because the vaccine has prevented those infections.

And so now we're looking, after month seven, at non-type disease and we have a situation where we have women who have been preferentially removed from the placebo group who are at the particularly higher risk for this infection.

Can I have slide 456, please? And so what we have here, I just want to show you who gets excluded from this population. Here's placebo and here's Gardasil. These are key parameters that have great relevance to risk of development of HPV infection. This is the group that starts naive to all four types

at day one. It's in a group like this that we evaluated replacement, but I want to show you how the placebo group gets a lot more people out. First of all, look, N = 443, N = 154. There is three fold greater number of placebo subjects that are removed, already a red flag. But who are these people? These are people that have a much higher risk of greater life time sexual partners, new partners within the six months prior, chlamydia, LSIL. So what we have here is a preferential removal of three times the population of people who are particularly at high risk for HPV infection and disease and we're looking at non-type after all of these people are removed. And it's for that reason that this analysis is confounded.

Replacement is a critical issue. And we have looked at replacement in populations that are defined, starting at day one and if I could have slide 223.

We asked the question in the longest term efficacy study that we have to date that was in the application about whether removal of the most common HPV type, HPV 16, would lead to an upsurge of new infections caused by other common HPV types that are not in the vaccine. The HPV 16 vaccine in protocol 005

allowed us to look at HPV 6, 11 and 18 infection. Here is the vaccine group, here is the placebo group. This is four years of follow-up and you can see that the infection rates are comparable between the two vaccination groups for persistent infection.

Infection is the first step in the development of cervical cancer and if there's an early warning with respect to replacement, we should see it there. And you can see that the event rates are the same.

And if I could have slide 224, please. We also looked in our phase III studies at disease and we asked among women who are naive at baseline, because see, replacement is something that will happen after the vaccine is given, right? So the question is, if you don't have -- among women who don't have disease at baseline, what's the rate of CIN not caused by the four vaccine HPV types? And you can see that the event rates are comparable for overall CIN, for CIN 1 and for CIN 2 and 3, comparable.

Can I have the next slide, please, 225? We looked at this also in our cervical cancer prevention trial. Again, women who are naive at baseline, looking at new infections, that would be so-

called replacement if they occurred, other than 6, 11, 16 and 18. Again, event rates were comparable between the vaccination groups.

So to date, we have no evidence for replacement, using analyses that take two equal risk populations and compare them.

I wanted also now to clarify Dr. Miller's comments about the MITT-3 population. The MITT-3 population is a population that we also looked at in the clinical trials. It includes women who are already infected at baseline.

If I could have slide 395. Now, women who are infected with HPV 16 or 18 at baseline should not benefit from this prophylactic vaccine. But they should get disease very soon after the onset of the trial. First of all, some of them already have CIN 2/3 at baseline. This population included anyone who was in the study at all. So even if you had HSIL at day one, you were included. So people with baseline disease were included, and of course, Gardasil will not shrink CIN 2/3.

The other question is will Gardasil impact infections already present? And this is a prophylactic vaccine. This is not what it's designed to do. So

what happens is that because these women are already prevalent infection and disease, you see that at the beginning of the trial we have a lot of disease in both the vaccination groups. But starting at month 12, the curves diverge and the curves become even more divergent over time and this is because the disease that's happening here is disease that's caused by new infections and these are the infections that Gardasil prevents. If you're infected at baseline with one HPV type, that -- the course of the infection with that one HPV type is not impacted. And this just points out the importance of vaccinating early, as in early age groups before exposure.

One of the other things that's important to understand is that women who are infected with one HPV type have a significant risk of being infected with the other three. And in our clinical trials, the event rate among women who were infected with one HPV type for the remaining three, was very high and the vaccine was highly efficacious in preventing it.

Now, one last comment -- two more comments. There was a question about whether paraffin-embedding changes the sensitivity of the assays. The answer to that is no. These assays are highly

validated. We can detect between six and 13 genomes of HPV. We've compared this to frozen biopsy PCR, where we just look at frozen tissue and check to see what HPV type is in the lesion, and sensitivity and specificity is the same.

And then finally, I want to ask for slide 235. There was already some discussion about this issue in boys. We have shown in our clinical studies in nine to 15 year old boys that anti-HPV GMT's were the highest in the program, two to three fold in younger women, higher than in girls even. The safety profile was favorable.

While we don't have efficacy in men and we're going to do that study and that study will not be impacted by decisions made today, we know that genital warts in men and women have a comparable histology, a comparable natural history. The disease is impacting hair-bearing characterized cells in both instances. While the shape of the organ is different, the skin is the same. And when you look specifically at external genital lesions, and I'm talking now about external vulvar lesions -- I'm not even talking about vaginal lesions, just vulvar, efficacy is 99 percent.

So the point that we're making is that

efficacy of Gardasil in men is highly likely to be significant.

Dr. Levin is going to come up and talk a little bit about notions of hurt immunity, about the vaccine. Go ahead, please.

DR. LEVIN: I can do it from here. Myron Levin, University of Colorado, School of Medicine.

Many people anticipate that the uptake of this vaccine will be delayed. We've heard one reason, maybe access, will be part of it, but the optimal uptake will be slower than some other vaccines have been, either for funding issues, maybe educational issues, and insofar as that happens, there will be a delay for us to achieve the optimal benefit of preventing cancers of these kinds in women, not only cervical cancer, but some of the other cancers that you've heard about and some that we haven't even emphasized in terms of the ero-digestive tract.

Insofar as we can prevent infection in men, if we can prevent infection in men, then we will indirectly provide protection for some of these women who are not immunized. Not only that, we will protect those men against extra-genital lesions. We will prevent the cancers that we know are due to HPV in men

and we will prevent some of the recurring laryngeopapillomatosis that men suffer from these infections.

So beyond that benefit, there will actually be a significant cost savings, in terms of preventing all of those infections in men and that, in turn, will impact on the cost benefit analysis that we have with this vaccine.

DR. FARLEY: Thank you. At this point, I'd like to invite Dr. Miller to proceed with presentation of the questions for the panel and then we will begin discussions.

DR. MILLER: Reviewing the questions, again, number one, did the data from studies 005, 007, 013 and 015 support the efficacy of Gardasil for the prevention of HPV 16, 18, related cervical cancer, cervical AIS and CIN 2/3 or worse in females 16 to 26 years of age?

Number two, do the data from studies 007, 013 and 015 support the efficacy of Gardasil for the prevention of HPV 6, 11, 16, 18, related VIN and VaIN 2/3 in females 16 to 26 years of age?

Number three, did the data from studies 007, 013 and 015 support the efficacy of Gardasil for

the prevention of HPV 6, 11, 16 and 18 related condyloma acuminata, VIN 1 and VaIN 1?

Four, did the immunogenicity data support bridging of the younger female population, nine to 15 years of age, to the efficacy population, females 16 to 26 years of age?

Number five, did the safety data from studies 007, 013, 015, 016 and 018 support the safety of Gardasil for use in females nine to 26 years of age?

And the last question for comment, please comment on post-marketing commitments.

DR. FARLEY: Thank you, Dr. Miller. Well, at this point, let me open it up for the panel. Rather than starting to present the questions, I think we need more time for discussion and we have representatives, both from FDA and the sponsor here and it looks like we have our first question from Dr. LaRussa.

DR. LARUSSA: This is a question for the sponsor. I want to go back to the immunogenicity issue. If this vaccine is used widely in younger age groups, there are likely going to be significant numbers who get one and two doses. So can you tell us something about geometric mean titers and sero-

prevalence rates after first and second dose, compared to third dose?

DR. BARR: If I could have just a second. Protocol 7, immunogenicity time-to-event curve over time, please. If you could show me the adolescent and adult time-to-event curve for protocol 7, please, 244, please.

Thank you. If you look at the post-dose one and post-dose two anti-HPV responses, you definitely have levels, but the levels are lower. We don't have any information on post-dose two anti-HPV responses over the long term because there are so very few people who actually didn't get more than -- got only two doses. One thing that I can point out is post-dose three, the levels do go up and you have this decline, but a stable plateau. This is adolescent data. Now we have month 18 data and you can see that the levels remain higher.

So although we don't have post-dose two data, we do have evidence to suggest that the immunogenicity of the vaccine in adolescents will be long term, higher even than what you see in adults.

DR. FARLEY: Dr. Greene.

DR. GREENE: If I could -- just a follow-up

on the immunogenicity question. There are different ways of expressing the data with respect to immunogenicity. One is the mean titers, as you have. The other is what percentage of patients failed to respond to some minimal titer level? And what I couldn't discern from the materials provided in advance of the meeting was how that minimum titer or how that minimum antibody titer level was determined when you reported the percentage of patients who didn't respond. Where did you derive that titer from?

DR. BARR: The -- so the answer to that is that it was the sero-conversion cut off. So in other words, seropositivity was defined as the number of women who developed -- or children, boys and girls, who developed an anti-HPV level above the sero-status cut off and the sero-status cut off was defined by looking at panels of completely naive individuals and the way we know that their children, PCR negative women, virginal -- women with zero sexual partners, and compared that with high -- with people with a lot of sexual activity, people with high grade lesions and looked at the differences between the antibody level and developed a cut off.

DR. GREENE: So then, it was not a level

that was determined by knowing that that was protective in some way?

DR. BARR: Correct. There is no minimum level that can be defined that says above this, you're protected, below this, you're not. Not yet. We need breakthroughs from the vaccine and the vaccine was highly efficacious.

DR. FARLEY: I have a question, again, for the sponsors, or several that have been -- bantered about with the open public hearing. I am assuming that you would continue to support screening for the cervical cancers that will not be excluded or not be prevented by this and I just wanted to hear your take on that.

And do you have a feeling for the two other areas of if they are women closer to being sexually active, do you have a feeling on whether they should be screened for pregnancy before being given the vaccine and the final is, whether you think that older -- within this age range that we're talking about, up to 26, that those who are older and statistically more likely to be seropositive or PCR positive at the time of being offered the vaccine currently, is there a role for screening for HPV positivity or for these four

sero-types, prior to giving the vaccine?

DR. BARR: I'll take them in order. First of all, I want to assure the Committee and the audience that this company is absolutely committed to cervical cancer screening and we will always be emphasizing the role of screening in the prevention of cervical cancer. This vaccine is not a replacement for cervical cancer screening and I think that's clear.

With respect to pregnancy, in our viewpoint, the overall -- the totality of the safety data point to the fact that Gardasil is highly unlikely to have been -- to impact pregnancy outcomes adversely, but we have not studied the vaccine in pregnant women.

So our view is that vaccination should be avoided in pregnant women and that in the course of typical interaction between a physician and his or her patient, there will be discussions about various medications that they are given and one of the questions might be to determine whether there is a possibility that the woman is pregnant. And on the basis of that, they can decide about further thoughts about what they should do, just in the event that they consider it. So for example, if she's potentially

pregnant -- if she's worried that she might be pregnant, that might be a good opportunity for a pregnancy test. But it's a discussion between the physician and her patient.

In terms of the question about screening prior to vaccination, a few comments. First of all, even if you're positive to one HPV type, you can derive benefit for the other three HPV types and it's very rare for women to be infected with two or three or four types simultaneously. And so even if you're somewhat older in the population, you still would derive benefit.

There is not a testing scheme right now for HPV specific typing. And even if there were, let's say you're HPV 18 positive, you could still derive benefit for HPV 16 prevention. Let's say you're HPV 16 positive. You could still derive benefit for HPV 18 prevention.

And so from our perspective and typically for vaccines, screening is not -- would be a difficult approach to be able to implement this on an individual basis or a population basis and substantial benefit could be denied to some women who might be infected with one type and could derive benefit from the other

three.

DR. FARLEY: Dr. LaRussa.

DR. LARUSSA: I may have missed this, but are you planning on giving us safety data in boys 16 and older and are you planning on studying males and females over 26?

DR. BARR: Yes and yes. We have an efficacy study in 16 to 26 year old men to evaluate for the impact on genital warts, infection and anal pre-cancer. We have a study -- and those data would be available only in late 2008. We have a study going on in mid-adult women above the age of 26 and those data will be available late next year.

DR. LARUSSA: What about the safety data on the boys, when will that be available?

DR. BARR: The nine to 15 year old boys, or the older boys?

DR. LARUSSA: Sixteen to 26.

DR. BARR: Because the study is blinded for long term efficacy follow-up, unfortunately the data will only be available in late 2008, along with the efficacy data.

DR. FARLEY: Dr. Maldonado.

DR. MALDONADO: Along those lines, that

means then that there is at least a three year gap between the vaccine becoming available right now as it is, to having these data in males? When you said available, you -- I assume that is your results.

DR. BARR: Right.

DR. MALDONADO: But you have to put a package together?

DR. BARR: That's right. So if we look at when the package insert will have information about male efficacy, that will be in 2009.

And so when we looked at -- we looked through our modeling work to determine what would be the impact of that kind of delay in cervical cancer rates and cervical pre-cancer rates? We saw that by delaying for three plus years, vaccination of boys, we could impact over 100,000 -- would could have an additional 100,000 CIN 2/3 cases that could have otherwise been avoided.

DR. FARLEY: Do you think the wide use and availability for both young males and females would interfere with your ability to accurately do an efficacy study, given your hope for hurt immunity effect?

DR. BARR: No, because the -- first of all,

we should be so lucky that updates are so high. But truth of the matter is, is that the -- if boys are vaccinated, it would be nine to 15 year olds, it would be a different age range. Furthermore, for the 16 to 26 year olds, they're already -- the male study, all the people are vaccinate and we're already through about one year of follow-up. So we're moving towards, by the time update starts to become more reasonable, we're going to be way close to the end of the clinical trial. We don't believe that there will be an impact. The impact would simply be on whether or not you're going to maximally start the train towards reducing cervical cancer rates in the population by vaccinating boys and girls, versus girls alone.

DR. FARLEY: Dr. Markowitz.

DR. MARKOWITZ: I have two questions. One, I wanted to get some more information on the post-marketing commitments and it looks there's going to be 5,000 women that will be included in the Nordic cancer follow-up study, and that's 5,000 women, half of those were vaccinated and half of those were in the placebo group, is that right? So there will be about 2,500?

DR. BARR: Two thousand five hundred per group and of course, they're going to get -- the

placebo will get vaccinated at the end of the study.

DR. MARKOWITZ: But in terms of the leading edge, in a sense, it will just be half?

DR. BARR: That's correct.

DR. MARKOWITZ: And could you comment on what the follow-up of women in the United States is going to be in any of your clinical trials?

DR. BARR: We are following -- in protocol 5, we will have reached 7.5 years of follow-up by the end of next year -- by the middle of next year, excuse me. And Dr. Koutsky, at her site, has actually looked at -- is going to be looking at the -- Dr. Koutsky had the largest amount of subjects, about 400 subjects, and we'll be looking at long term infection, efficacy in that population.

In the United States itself, from the phase III studies, we don't have any plans right now to follow up the women in the clinical trial and the reason for that is that this is mostly -- that women were recruited primarily in college campuses. At this stage, they are starting to leave and head off to their next stage in their lives and it's very difficult to do that. That's why we chose to evaluate the population in Scandinavia.

I would point out that the adolescents' sentinel cohort is about 40 percent U.S. children and that population was going to be followed for at least six years plus. That's a population nine to 15 years old.

DR. MARKOWITZ: Can you give us, as a follow-up to that, a sense of the demographic diversity in that group?

DR. BARR: In the women in --

DR. MARKOWITZ: In the U.S. population that you are going to follow.

DR. BARR: Certainly. The U.S. population -- can I have the slide looking at the efficacy population, ethnicity? It would be 269, please.

This is the efficacy population and this is the -- sorry, slide 269, please, sorry. We just broke down the population in the efficacy by ethnic group and I think that you can see that there is about 70 percent are Caucasian and then the rest are, there's Hispanic, African decent, Asians and others.

DR. MARKOWITZ: I'm sorry, just to follow up again on this one issue. In terms of looking --

DR. FARLEY: Dr. Markowitz is speaking.

DR. MARKOWITZ: Looking at serologic

correlates of protection, do you anticipate getting those data then from the Nordic follow-up studies?

DR. BARR: Yes. Well, from -- that's just one of the studies that we're going to get, this kind of data. The first -- that study is important because it will get us very ultra long term efficacy data.

The other piece -- and again, serology at year five and 10. We have serology at the end of the phase III studies and I mean, we're going to be following these women out, so we'll be able to look at what their last one was before they left the study.

The other piece is the adolescent immunogenicity cohort and what's going to happen with that cohort is that upon their sixteenth birthday, they're going to start to get effectiveness evaluations. In other words, they're going to start to get screened and stuff like that.

So we're going to have immunogenicity that starts at a median age of 12 and then goes on for four, five or six years. And I think it will be a very interesting population to evaluate and real time -- I mean, the real world kind of approach of vaccinating adolescents and then looking at their efficacy over time. Those data would be available about two and a

half to three years ahead of the general population, on a timed basis.

DR. GREENE: Can I just ask one more question? I had one other question. With respect to, I understand that when a patient became a case, she was censored in your data analysis. What I couldn't easily discern, again, from the initial -- preparatory information that we had prior to the meeting, was how many women were lost to follow-up in the later portion of the follow-up period and what, if any, assumptions were made with respect to their outcomes? Was it a last observation carried forward kind of an analysis, because obviously, for something like this where there's a significant latency between when an infection would occur and when an event would be expected, having person years early on, even if you have lots of them, would not be as valuable, as person years later on.

DR. BARR: I'm going to ask Dr. Lupinacci from the Biostatistics Group to answer that question.

DR. LUPINACCI: Yes, first of all, our discontinuation rates in phase III are very small. At this point, in protocol 013, 93 percent of the subjects are still continuing the study. In protocol 015, 97 percent of the subjects are continuing.

In our primary analysis we simply follow subjects until they discontinue the study and they are able to be counted as end points, based on any data up until the time they discontinue.

However, due to the concern that you have raised, we did perform imputation analyses post-discontinuation in the subjects who were lost to follow-up and the way that we did that was to assume the placebo event rate, the time following discontinuation in both groups, which is conservative because that assumes no vaccine efficacy in those subjects following the time of discontinuation, and the results of that efficacy analysis, basically added one case to each group. So the reduction in vaccine efficacy estimate was minimal.

DR. FARLEY: I think Dr. Emerson has a question.

DR. EMERSON: I'd like to just return to the bias question. Can we see those slides again, please?

DR. BARR: Do you want to look at -- which one?

DR. EMERSON: I'd like --

DR. BARR: The graph? Okay, sure, 456,

please. Yes, sir.

DR. EMERSON: Okay, now, so we've got a difference of about 300 patients that were excluded that have a propensity to be a -- the higher risk categories. Did you do any sort of a propensity score analysis or anything like that, in order to deal with this issue and see whether that does, in fact, explain the differences that you've seen in this analysis?

DR. BARR: We didn't look at this specific analysis, but we did look at what were the characteristics of individuals who developed a case and people with greater than three life time sexual partners, greater than one partner in the prior six months, had a substantially higher rate of developing a case, compared to those -- the odds ratios were much higher in that population. We did not look at the specific population.

DR. GREENE: But rather than being on an odds ratio scale, on sort of an incidents rate, do you have --

DR. BARR: I don't have those numbers. Dr. Koutsky, can you just comment on the -- how these kinds of numbers might impact the event rates, perhaps, greater than three life time partners versus none.

DR. KOUTSKY: Laura Koutsky, University of Washington. The strongest risk factor for acquisition of HPV and for development of dysplasia, external -- outside of HPV, high risk HPV types is number of partners and also, having another STD is a very important risk factor. It turns out that STD's tend to travel together. If you get one STD -- if you get one HPV infection, you're more likely to get another HPV infection.

So once you start excluding people who have infections due to certain types, you're excluding people who are at risk for disease on the basis of having one infection, because they're more likely to be having sex with partners who are exposing them to other HPV types as well.

DR. GREENE: But can you give me an idea, out of those 200 patients, how many cases would you expect to have?

DR. BARR: What I can show you is, I can show you if we did the analysis, looking just at the people who are naive to all four types of baseline, what were their results. Is that slide 1035 or 1025?

So this is without the excluded subjects. This is just looking at the people who are naive at

baseline. And the point that we're making here is that the -- we have tiny -- I mean, the numbers are pretty much the same.

So you went from --

DR. GREENE: So if I read those numbers correctly, that difference in cases of seven, as compared to the 10, that we are seeing roughly, in the other analysis --

DR. BARR: There are -- no, they are much smaller, but it's a much smaller population. So in the percent reduction, therefore, the percent excess becomes much greater. Your denominators and subject years are different.

So if you want to look at the -- I'm sorry, Dr. Lupinacci has something to add.

DR. LUPINACCI: I was just going to say that we actually haven't looked specifically at the analysis, the question that you're asking.

DR. BARR: But the point that I'm trying to make is that the denominators that you have there, the percent reduction is dependent on person time. So the percent reduction that you see in that population is a much smaller number than the numbers that you have in the all MITT population.

And in every time when you looked at things without having to exclude out individuals from day one through month seven, because we're looking at incident disease looking forward, we never saw any replacement. It's that analysis and that analysis only that showed an imbalance and that imbalance could be explained by this enormous removal of particularly high risk people. You have to understand that even in the highest risk population -- I mean, even in the entire population, only several hundred people out of several thousand people got disease and they were all people with high risk. So I mean, you're --

DR. EMERSON: I agree, I just think that there's a lot that's being invoked here, just to look at those numbers and then for us to take on faith that that's the explanation for all of the difference.

And where all of this -- you know, goes with this, that an awful lot of our belief in this end point, and by the way, I'm not really saying I disbelieve this end point, but just that you have to consider the fact that we're accepting absolutely the statement that getting this pre-malignant transformation in the presence of HPV 16, that again, we're just at this risk of have we reduced the end

point to just looking to see whether we prevent infection, rather than preventing the cancer and -- that the whole logic flow is that we're attributing the pre-malignant transformation to a specific type and I will concede straight out that it really looks like your vaccine stops the HPV 16, 18 and that's set.

But the question is, is that just the sign and that by our end point is just saying that it's attributable to HPV 16? Well, of course, if we're getting the same sorts of pre-malignant transformations, but we've removed those infections, we're really just testing whether it's an infection end point.

DR. KOUTSKY: I'll comment on this. I'm not sure if what you're getting at is the issue of is CIN 2/3 really a pre-cancerous lesion?

DR. EMERSON: No, it's this concept of the attributing certain of the CIN 2/3's to being caused by 16 and 18 and that that's all you're being held responsible for. And I guess -- and I'm gathering that this word replacement that you're using is this concept of whether we're just attaching a different label to it. But I'm not invoking that it's not some other new disease that's coming up. I'm just calling that we're

labeling it differently. It's almost the treating the symptom, but not the disease sort of idea.

DR. KOUTSKY: I think that's wrong and I think it's wrong particularly because the pathologist who read the histology are experts in gynecologic pathology and they're reading it the same as they read the routine clinical pathology and they're blinded to what type is present. There is that information in terms of detection of the CIN 2/3's and I think the other stuff that, it is the CIN 2/3 that you detect in screening and treat and when you remove that lesion, and there have been hundreds of studies showing that about 50 percent of CIN 2/3 is HPV 16 positive, and it is the 16 or 18 that's causing the lesions --

DR. EMERSON: Well, now, again, that's a presumption that it's causing it. You can't --

DR. KOUTSKY: I don't think so. I think that's --

DR. EMERSON: It's got to be observational data because it's -- and the best we're going to have, and I'm not really objecting to the entirely. But there is this aspect of the documentation of whether -- you know, your primary end point is, as long as you can -- you could actually -- with your primary end point,

just your primary end point and we won't look at any other analyses. Of course, we did look at the other ones, but just with -- with your primary end point, you could have actually caused cervical cancer, but as long you prevented 16/18 to being -- to showing up at the same time, you could count that as a success.

DR. KOUTSKY: Biologically, what you're saying doesn't make sense to me.

DR. EMERSON: Well, except --

DR. KOUTKSY: Perhaps Dr. Unger could speak to this.

DR. EMERSON: Well, so I can agree that the un-intervened state, we have these correlations. The question that's in my mind is has there been any idea that there's people co-infected with two different types that would lead to cancer, that in the placebo group, because 16 is present, we're calling that a failure and because your vaccine successfully blocks the 16, but not the other cause, that that's just not showing up in your -- in the vaccine group. And it's not really a qualitative thing that I'm worrying about, as much now it's quantitative. I think it's clear that there's -- that probably that magnitude of effect is not enough to make a strong difference. But I think

that there is some suggestion in the crude analyses that we can do, that there's some level there.

DR. FARLEY: Dr. Unger, would you like to respond?

DR. UNGER: Well, I think there's a couple of different issues and one is to do with the data that's available for causality. In addition to the epidemiologic data which is observational, there's a lot of basic science data that really does demonstrate that the oncogenes' expression induces all the changes that you would expect. There's lots of model systems that have shown this.

So I think on a population basis, there really is little doubt that HPV 16, for example, is associated with -- in causing cancer.

Now, in an individual, you always have the possibility of multiple types being present and one of the difficulties with using an HPV detection as an end point is the fact, was it really associated with the tissue? Was it just -- happened to be there? I think the approach of actually looking for HPV within the tissue is about as good as you can get. And the approach of doing the sandwich so that you actually are getting tissue that's representative of a lesion, it

still is, I guess, a concern and I'm assuming you're going to have data on all of the HPV types that are -- that they are able to detect within that tissue.

But given the prevalence of HPV 16 in the general population, the numbers that they're seeing, it all is very, very reasonable. The unlikely that all of these would be due to some other type with HPV 16 also being there, but I -- and I do think that it's going to be important to do some sort of an assay to look at all of the HPV types within these lesions, just to be -- sort of put all the little dots on the I's and cross all the little T's to be sure of what's there. But I think this was a very reasonable approach to trying to demonstrate.

DR. EMERSON: What is the prevalence of 16/18 relative to the other types that were listed as -- causative of cervical cancer?

DR. UNGER: Well, it depends on the population, unfortunately, so that, I don't have a really good answer. In a lot of populations, in most populations, general populations, HPV 16 is the most prevalent in the general population. So it's a very prevalent infection.

What you see is that with increasing

disease and increasing behavioral risk, that proportion of HPV 16 kind of increases proportionately, so that, whereas, for example, in a general population it might be on the order of 10 percent. When you get up into CIN 3's, it's more like 50 percent.

DR. EMERSON: Is that prevalence in the person, or is that prevalence in the lesion itself?

DR. UNGER: It's prevalence in the person. Most of the data is on prevalence in the person, but when people have looked at tissues, they've found that the correlation is very good, not perfect, but very good.

DR. FARLEY: Yes, comment from Dr. Goldenthal.

DR. GOLDENTHAL: I just wanted to comment on one of the analyses that I found to be, in certain regards, the most informative analysis and this was a separate analysis done on protocol 005. And as you may recall, that was the protocol where there was the most follow-up. In other words, subjects had three years of follow-up, approximately, after the third dose of vaccine and there was one particular analysis where the sponsor looked at efficacy against CIN 2 or worse, due to any HPV type in the MITT-3 population. In other

words, people who were -- which didn't exclude people who were seropositive and/or PCR positive at baseline. In other words, it was the total population starting one month after the first dose. And in that particular analysis, again with the longer follow-up, the efficacy for CIN 2 or worse was a point estimate of 45 percent at that longer time point with confidence intervals of 11 to 67 percent for the 95 percent confidence intervals.

So I found that analysis to be one of the more informative analysis in terms of looking at the overall issue of you know, again, they were including any CIN 2/3 due to any HPV type.

DR. EMERSON: And so that analysis would be more comparable with the one that they did that was sort of projecting that a 99 percent efficacy for infection in a naive population should lead to roughly the 55 percent, if you recall from their presentation, that they were -- did such an analysis of what the efficacy should be.

DR. FARLEY: Any other comments or questions or discussion points?

(No verbal response)

DR. FARLEY: At this point, we could do one

of two things. We could take a five minute break, if people feel they needed -- oh, Dr. Markowitz has another comment.

DR. MARKOWITZ: I just wanted to make a comment on the issue of male vaccination and comment something that Eliav said, that Dr. Barr said, in terms of modeling. I think we haven't seen the modeling data at this meeting, so it's hard to, I think, evoke some of the modeling data to comment on the percent of cases of CIN that would be presented. I mean, there's a lot of assumptions that have gone into a lot of the different models that have been done and I think that the potential for using this vaccine in males is very exciting, and potentially exciting when we have the data. But I don't think we should use, right now, unless we have the modeling data to make that decision.

And I think that in terms of the number of cases of CIN that get prevented between now and three years from now in women, a lot of that is going to be depending on giving this expensive vaccine to women, which is going to be a hurdle in terms of some programmatic issues. So anyway, I just wanted to make that comment in terms of the argument of the modeling data, which we haven't really seen.

DR. FARLEY: Dr. Noller.

DR. NOLLER: Just to be sure I'm right, we are not being asked either by the sponsor or FDA to make any statement about males today, is that right?

DR. FARLEY: Our questions are specifically for --

DR. NOLLER: For females.

DR. FARLEY: -- for females.

DR. NOLLER: I just wanted to be sure.

DR. FARLEY: And these are questions that are being asked of us by the FDA. Yes?

MS. KRIVACIC: I have one more question for the sponsor, and that is, the efficacy study that you mentioned you will be doing into next year in older women, can you comment on that in terms of the age range and then also, if you will be looking at PCR analysis on potential other HPV types for those women?

DR. BARR: Yes, the age range is going to be 26 to 45 years old, sort of right up to the perimenopausal time and we're going to be evaluating primarily for vaccine types, but we also will be looking at other non-vaccine types. But again, in the same tiered sort of approach of availability.

MS. KRIVACIC: And is that in the U.S.?

DR. BARR: Yes, those -- it's like all of our studies. A good proportion of them are in American women, but we also have a proportion in Europe and in other parts of the world, South America.

MS. KRIVACIC: Thank you.

DR. FARLEY: And that was Susan Krivacic, our patient representative's question. Okay, so we -- Dr. Royal?

DR. ROYAL: Since there was a mention of PCR brought up again, I'd just like to say that it would be nice to see the PCR data. It's so counter-intuitive that paraffin-embedded tissue would show the same copy numbers as frozen tissue, given the fact that a frozen sample of the highest quality DNA, just by thawing it, will cause you to lose copies. It would be good to know that you are using a highly sensitive assay in that, you're not seeing six to 10 copies, when you should be seeing 50 to 100.

DR. FARLEY: Is this a response?

MS. BRYAN: Janine Bryan. I'm in the Basic Research portion of Merck. And I think it would be best just to show you slide 1409. This is the limited detection of our assay. What we've done is taken, in this case -- again, we haven't really explained our

assay, but most genotyping assays look at just one gene and we look at three. And what we have done for this case is took a look at the limited detection, is to take cloned sequences and know the copy number and then from that we can back down and know by dilution of that, what copies we have. And we've reproduced this between six and eight times for each type and for each gene.

And as you can see, I think that between about six and 12, depending on the variability here, copies per gene that we can see.

I think also to convince you, can I have slide 1408? This is just a picture to show you that this is an amazingly sensitive assay and we have a huge dynamic range. We can detect over six different logs and we can really be very, very confident in our results because we have three genes and a very rigorous way of saying that something is positive. Something is positive only if we can be able to detect it in at least two genes and at least two sites. So we do -- when we do swabs, we have to detect it in both swabs or if we can only detect it in one swab, we have to be able to reproduce that. So we're very, very confident in our detection.

DR. FARLEY: Yes, Dr. Unger.

DR. UNGER: I think it would be -- the question that he was really asking was the -- that was in plasma DNA, which is again optimal. Have you looked at the copy numbers that you get in the frozen tissue versus the paraffin embedded, and I'm sure model studies, you must have looked at something like that.

MS. BRYAN: I don't actually have a slide to address that, but what we actually did was take biopsies and literally split them and freeze one and section the other and then went to see whether or not we could detect. And because of the fact that tissue it not uniform and HPV is only going to infect the epithelial tissue and it's going to be very selective as to which portion, it really isn't fair to say that in this half, you get -- we detected 30 copies and in this half, we only detected five copies, because in this half we might have had a heck of a lot more dermal tissue.

So we tried to balance that out with looking at betaglobin controls, but that again would still be positive for dermal tissue. So when we base it on detection levels and multiple samples, we were able to say that their detection rates were comparable

between the two.

DR. FARLEY: Okay. Any last discussion? Dr. LaRussa.

DR. LARUSSA: Just, could you clarify one thing you said about PCR positivity? If the study woman had more than one swab and one was HPV positive, but the other was not, how was she classified?

Ms. BRYAN: Okay. Depending on the protocol, we either took two or three swabs every time that we were sampling. So one was endoectocervical and one was lavial vaginal or vulval. External swabs -- let's put it that way. It is possible that someone would have, especially if you were looking at 6 and 11, would only be the external or any other.

So what we did was, we still wanted to prove positive. So when the sample would come to the clinical receiving, it was aliquotted, okay. And when we would receive it in the lab we would extract the DNA from one aliquot and look at the detection of the three genes. If we showed that it was positive in that swab, but not the adjacent EEC swab, then we would have to recall another aliquot of that same swab and prove it again.

DR. FARLEY: Okay. Well, I have concerns

that we may lose members if we break, so that if people -- well, I mean, in terms of flights and such things, not for lack of interest, by any means. So I would propose that we proceed directly to the votes on the questions at this point, unless there are any strong objections. Any strong objections?

(No verbal response)

DR. FARLEY: Okay. Well, the process we'll go through is going around and having each member register their vote for each individual question. We have two non-voting members on the panel today, Dr. Maldonado, who is an industry representative and who is a non-voting member who we will invite to comment, if he wishes, and Dr. Lauri Markowitz from CDC is also a non-voting member and who also can add any comments that she would like to.

So otherwise, we'll go around and let's start with the first question, and for the first round, we'll start with you, Dr. Royal.

So the first question that we're being posed is do the data from studies 005, 007, 013 and 015 support the efficacy of Gardasil for the prevention of HPV 16, 18, related cervical cancer, cervical AIS and CIN 2/3 or worse in females 16 to 26 years of age? So

Dr. Royal.

DR. ROYAL: I do believe that the vaccine does protect. The data from those studies do demonstrate protection from those HPV sub-types against cervical AIS, CIN 2/3, overall. But I do still harbor concerns about the sub-group that was shown that was seropositive for antibody and also PCR positive in whom there appear to be, perhaps a trend towards a greater frequency of disease development.

DR. FARLEY: So you're voting yes.

DR. ROYAL: Yes, with that caveat.

DR. FARLEY: Thank you.

DR. ROYAL: That qualifier.

DR. FARLEY: Dr. Noller.

DR. NOLLER: I believe that the data strongly supports the efficacy of Gardasil for the conditions listed, so I vote yes.

DR. FARLEY: Thank you. Dr. Greene.

DR. GREENE: Yes.

DR. FARLEY: Thank you. Dr. McInnes.

DR. MCINNES: Yes.

DR. FARLEY: Ms. Province.

MS. PROVINCE: I believe the data do support the efficacy and I vote yes.

DR. FARLEY: Thank you. Dr. Gellin.

DR. GELLIN: Yes.

DR. FARLEY: Dr. LaRussa.

DR. LARUSSA: Yes, in the naive women.

DR. FARLEY: Dr. Wharton.

DR. WHARTON: Yes.

DR. FARLEY: Would you like to make a comment, Dr. Markowitz, at this point? No, okay. Dr. Unger.

DR. UNGER: Yes.

DR. FARLEY: Dr. Word.

DR. WORD: Yes.

DR. FARLEY: Ms. Krivacic.

MS. KRIVACIC: Yes.

DR. FARLEY: Dr. Emerson.

DR. EMERSON: Yes.

DR. FARLEY: And I will also vote yes for those specified within this question, particularly -- or specifically, the naive point as shown in the studies.

MS. WALSH: Totals, total votes from members for question number one, 13 votes, 13 votes yes, zero no, zero abstained.

DR. FARLEY: Thank you. Now, we'll proceed

to the second question, which is do the data from study 007, 013, 015 and 015 support the efficacy of Gardasil for the prevention of HPV 6, 11, 16 and 18, related VIN 2/3 and VaIN 2/3 in females 16 to 26 years of age? And this time, why don't we start with Dr. LaRussa.

DR. LARUSSA: Same comment, yes, and in naive women.

DR. FARLEY: Thank you. Dr. Wharton.

DR. WHARTON: Yes.

DR. FARLEY: Dr. Unger.

DR. UNGER: Yes.

DR. FARLEY: Dr. Word.

DR. WORD: Yes.

DR. FARLEY: Ms. Krivacic.

MS. KRIVACIC: Yes.

DR. FARLEY: Dr. Emerson.

DR. EMERSON: Yes.

DR. FARLEY: Dr. Royal.

DR. ROYAL: Yes, and the naive group.

DR. FARLEY: Dr. Noller.

DR. NOLLER: Yes.

DR. FARLEY: Dr. Greene.

DR. GREENE: Yes.

DR. FARLEY: Dr. McInnes.

DR. MCINNES: Yes.

DR. FARLEY: Ms. Province.

MS. PROVINCE: Yes.

DR. FARLEY: Dr. Gellin.

DR. GELLIN: Yes.

DR. FARLEY: I will also vote yes on this question. Any other comments? I guess we don't have Dr. Maldonado. Any comments from Dr. Markowitz? No, okay. Thank you.

MS. WALSH: Voting totals for question number two, 13 votes yes, zero votes no, zero votes abstained.

DR. FARLEY: Our next question, number three, do the data from studies 007, 013 and 015 support the efficacy of Gardasil for the prevention of HPV 6, 11, 16, 18, related condyloma acuminata, VIN 1 and VaIN 1? Dr. Royal.

DR. ROYAL: I vote yes.

DR. FARLEY: Dr. Noller.

DR. NOLLER: Yes.

DR. FARLEY: Dr. Greene.

DR. GREENE: Yes.

DR. FARLEY: Dr. McInnes.

DR. MCINNES: Yes.

DR. FARLEY: Ms. Province.

MS. PROVINCE: Yes.

DR. FARLEY: Dr. Gellin.

DR. GELLIN: Yes.

DR. FARLEY: Dr. LaRussa.

DR. LARUSSA: Yes.

DR. FARLEY: Dr. Wharton.

DR. WHARTON: Yes.

DR. FARLEY: Dr. Unger.

DR. UNGER: Yes.

DR. FARLEY: Dr. Word.

DR. WORD: Yes.

DR. FARLEY: Ms. Krivacic.

MS. KRIVACIC: Yes.

DR. FARLEY: And Dr. Emerson.

DR. EMERSON: Yes.

DR. FARLEY: And Dr. Farley, I also vote yes on this question. Any other comments from non-voting members?

MS. WALSH: Total votes, question number three, 13 votes yes, zero no, zero votes abstained.

DR. FARLEY: Question number four, do the immunogenicity data support bridging of the younger female population, that is nine to 15 years of age, to

the efficacy population in females 16 to 26 years of age? We'll start with Dr. LaRussa.

DR. LARUSSA: Yes.

DR. FARLEY: Dr. Wharton.

DR. WHARTON: Yes.

DR. FARLEY: Dr. Unger.

DR. UNGER: Yes.

DR. FARLEY: Dr. Word.

DR. WORD: Yes.

DR. FARLEY: Ms. Krivacic.

MS. KRIVACIC: Yes.

DR. FARLEY: Dr. Emerson.

DR. EMERSON: Yes.

DR. FARLEY: Dr. Royal.

DR. ROYAL: Yes.

DR. FARLEY: Dr. Noller.

DR. NOLLER: Yes.

DR. FARLEY: Dr. Greene.

DR. GREENE: Yes.

DR. FARLEY: Dr. McInnes.

DR. MCINNES: Yes.

DR. FARLEY: Ms. Province.

MS. PROVINCE: Yes.

DR. FARLEY: Dr. Gellin.

DR. GELLIN: Yes.

DR. FARLEY: And I also register a vote of yes on this question.

MS. WALSH: Total votes, question number four, 13 votes yes, zero votes no, zero votes abstained.

DR. FARLEY: Question number five is, do the safety data from study 007, 013, 015, 016 and 018 support the safety of Gardasil for use in females nine to 26 years of age? Dr. Royal.

DR. ROYAL: Yes.

DR. FARLEY: Dr. Noller.

DR. NOLLER: Yes.

DR. FARLEY: Dr. Greene.

DR. GREENE: Yes.

DR. FARLEY: Dr. McInnes.

DR. MCINNES: Yes.

DR. FARLEY: Ms. Province.

MS. PROVINCE: Yes.

DR. FARLEY: Dr. Gellin.

DR. GELLIN: Yes.

DR. FARLEY: Dr. LaRussa.

DR. LARUSSA: Yes.

DR. FARLEY: Dr. Wharton.

DR. WHARTON: Yes.

DR. FARLEY: Dr. Unger.

DR. UNGER: Yes.

DR. FARLEY: Dr. Word.

DR. WORD: Yes.

DR. FARLEY: Ms. Krivacic.

MS. KRIVACIC: Yes.

DR. FARLEY: Dr. Emerson.

DR. EMERSON: Yes.

DR. FARLEY: And again, I vote yes on this question as well. Any comments? No comments.

MS. WALSH: Total votes, question number five, 13 votes yes, zero votes no, zero votes abstained.

DR. FARLEY: Okay, and the final request is for comment on post-marketing commitments. I think we've had a fair amount of discussion. There's been a lot of description of plans that are in place or intended to be put in place, but if -- are we required to go around individually, or do we want to open this for people who have suggestions or want to designate specific post-marketing commitments? Dr. Emerson.

DR. EMERSON: I guess just two areas. One is, in the sponsor's original presentation, they gave a

slide that made me think that they were trying to claim that the vaccine wouldn't somehow remove the burden of screening on the population and I don't think that it does that at all and I would certainly hope that there would be something in the label to absolutely make clear that the screening still has to go on, and this is tied-in in part to my second comment, which again is, as I've been remarking on this end point that we have is really driven primarily, in terms of evidence, by the effect on infection and then by our belief that we can ascribe individual causality of a particular type. And so the statements about 70 percent of the cervical cancer being, therefore, protected against if we are to believe the 100 percent efficacy point estimate or even the 75 percent to 100 percent confidence interval. It may well be over-stated in this regard. And so I just think that there C- that some post-marketing to really get estimates on how the distribution of the cases that do show up despite the vaccine is very important.

DR. FARLEY: I agree and I would like to encourage. I think that the idea of the long term surveillance for the longevity of protection, as well as the outcomes over time is very important. And I

think that the Nordic study is an ideal situation and certainly one that I'm very supportive of. I also have minor concerns that it may or may not be necessarily representative of what we might see in underserved populations in the U.S. population, a more diverse population genetically, as well as socioeconomically and would encourage the surveillance systems to be strongly inclusive of those who represent the U.S. population at risk.

And also, agree with the idea conceptually of anything that we can do to encourage availability of this vaccine to those at highest risk. Dr. Noller.

DR. NOLLER: I'd like to make a comment that's probably addressed to FDA more than the sponsor, but based on their presentation where they stressed the success of the vaccine in the naive population, underlining and bold-facing some of the comments, from the clinical standpoint, it's virtually impossible to do testing for the -- serotesting for immunity to HPV. There's no such test readily available and if it were, it would prohibitively expensive. So I hope we don't emphasize that. Certainly, the vaccine is aimed at the naive men and women, women now. But I don't think we want to emphasize that too much or there will be too

many questions about should we do sero-typing? And that's just not available. It will just confuse people, I'm afraid.

DR. FARLEY: Dr. McInnes.

DR. MCINNES: I wanted to just respond to the question that I thought that the plans that had been laid out by the sponsor showed a real sensitivity to the need to continue to collect data, specific types and showed a commitment having to respond to a collection of those data. I think from a programmatic implementation piece, there aren't going to be questions around what may down the line be boosting requirements that would speak to vaccination regimens and I think collection of those sorts of data that could inform on a very practical and pragmatic level are going to be looked to.

And in addition, I think this question that has started to raise its head and will continue to is potentially down the line, the addition of other HPV types and any sort of data that might be gathered with high specificity that would speak to the feasibility of increasing the valency of the vaccine would be welcome.

DR. FARLEY: Dr. Word.

DR. WORD: Actually, my concern was related

to the replacement types, and so it's already been stated. I don't need to reiterate it.

I guess the other thing too that's always -- and maybe it's not our privy, but I guess it keeps bothering me. I know this is really directed towards women who are, as you say, haven't had a sexual debut yet. They are sexually naive. However, if you -- but adolescents don't tell the truth all the time and I know you're not routinely screening for people for different types, but what happens if it begins to go backwards on you, like suddenly you have all these women who are now CIN 2 and 3's and someone says to you well, the vaccine really didn't protect me, but I actually had it. But then the reality of it is, maybe it did, but no one ever just bothered to look to see if they were infected before. Is there -- I don't know how to approach that, because I guess I'm thinking about it long term if someone approached me later on to say how would I look at that? I know it's an enormous task and it's probably out of our purview, but I don't know if it's something you thought of long term, but -- I'm rambling on now, but I'm going back to replacement issue too.

I think with the replacements, I'm

interested to find out, I'm not as worried. We had pneumococcal vaccine come, we dropped certain sero-types and replaced them with others and we're starting to see more, but we haven't come back up to that same high rate. Maybe we won't have it with this one either, since you've identified two major ones, but it would be nice just to find out what you're doing.

DR. FARLEY: Well, I think this, again, further emphasizes the need for continued screening, that we don't give up aggressively looking for cervical dysplasia and cervical abnormalities, despite the introduction of this vaccine. Ms. Krivacic.

MS. KRIVACIC: I have a comment to what Dr. Word's saying. I think as you move forward with your labeling, as a former cancer patient myself, I think one of the things to be very cognizant of is putting something in the labeling where you're saying it is a vaccine to prevent these HPV diseases, which are related to potentially causing cervical cancer. You don't want to get to a point where maybe down the road, a lot of patients will be still developing cervical cancer and saying, "Oh my God, why did I take this vaccine and it's not working?" In other words, setting up sort of a false hope scenario. It's just a comment.

MS. PROVINCE: Yes, I just want to echo the concerns that have been expressed about continued screening and I think we just can't emphasize that enough and especially in terms of the labeling issues, that people understand fully that the vaccine is not a replacement for screening and I think there is a real concern there.

And then just, I want to emphasize, as others have, that a need for continuing post-market surveillance and in terms of adverse events, including possible rare or very rare adverse events and then, just the whole issue of continuing protection. Thank you.

DR. FARLEY: Other comments.

(No verbal response)

DR. FARLEY: Well, I would like, in closing, to just say that this has been one of the most complex and difficult to structure series of clinical trials that the sponsor has had to put together and execute and produce some very impressive data and this is involving screening and biopsies and PCR and such. It's truly incredible that it's come to this point and that it has been carried to this point and we now see the results that we see today and it is exciting that

we will have now one more entry into and one foot forward in the progress towards, eventually, hopefully eradicating all cervical cancer, but this is certainly a wonderful, good step in addition to our screening process that we have available.

So thank you to all the panel, to all of the sponsors, participants and to the FDA and to all who gave very good input from the open public hearing as well. The meeting is now adjourned.

(Whereupon, the foregoing presentation was concluded at approximately 3:20 p.m.)