UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

100th MEETING
OPEN SESSION

THURSDAY,
SEPTEMBER 23, 2004

The Advisory Committee met at 9:00 a.m. in the Versailles Ballroom of the Holiday Inn Select, 8120 Wisconsin Avenue, Bethesda, Maryland, Dr. Gary D. Overturf, Chair, presiding.

PRESENT:

GARY D. OVERTURF, M.D.	Chair
MONICA M. FARLEY, M.D.	Member
BRUCE GELLIN, M.D., M.P.H.	Temporary Voting Member
RUTH A. KARRON, M.D.	Member
DAVID M. MARKOVITZ, M.D.	Member
PAMELA McINNES, D.D.S.	Temporary Voting Member
STEPHEN PETTEWAY, Jr., Ph.D.	Acting Industry Representative
CINDY LYN PROVINCE, R.N., M.S.N.	Consumer Representative
WALTER ROYAL III, M.D.	Member
DAVID STEPHENS, M.D.	Temporary Voting Member
RICHARD WHITLEY, M.D.	Member
BONNIE M. WORD, M.D.	Member
CHRISTINE WALSH, R.N.	Executive Secretary

FDA REPRESENTATIVES:

JOSEPH TOERNER, M.D., M.P.H.

SPONSOR REPRESENTATIVES:

COL. DEBORAH BIRX
LTC ARTHUR BROWN
LTC JEROME KIM
PRASERT THONGCHAROEN
SUPACHAI RERKS-NGARM

I-N-D-E-X

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

9:03 a.m.

CHAIRMAN OVERTURF: Good morning. I'd like to welcome you to the second day of the Vaccine and Related Biological Products Advisory Committee meeting. This is an open session, and, first of all, I'll turn the meeting over to Christine Walsh who has some announcements.

MS. WALSH: Good morning. I'm Christine Walsh, the Executive Secretary for the Vaccines and Related Biological Products Advisory Committee. This brief announcement is in addition to the conflict of interest statement read at the beginning of the meeting on September 22 and will be part of the public record for the Vaccines and Related Biological Products Advisory Committee meeting on September 23, 2004.

This announcement addresses conflict of interest for Topic 2. Drs. Bruce Gellin, Pamela McInnes and David Stephens have been appointed as temporary voting members for this topic. Dr. Stephen Petteway is participating as a non-voting industry

representative, acting on behalf of regulated industry. The Food and Drug Administration has approved waivers under 21 USC 355(n)(4) of Section 505 of the Food and Drug Administration Modernization Act for Dr. David Stephens. Dr. Steven Self has recused himself from participating in this discussion. That ends the reading of the conflict of interest statement.

Dr. Overturf, I turn the meeting over to you.

CHAIRMAN OVERTURF: The purpose of this meeting is to review the Thailand HIV vaccine phase III trial. The trial sponsor being the Office of the Surgeon General and the U.S. Army. The products are an HIV I recombinant canarypox-vectored vaccine and a recombinant gp 120 B/E CHO cells with alum vaccine. And I'm going to ask, first of all, Dr. Joseph Toerner, who will be the first presenter, to come to the podium.

DR. TOERNER: Good morning. My name is Joe Toerner. I'm a Medical Officer in the Division of Vaccines and related product application at CBER, and

I wanted to welcome you all today to today's discussion at the VRBPAC. In particular, I'd like to recognize and welcome the sponsor who has included colleagues from Thailand who will be participating in today's VRBPAC session and would like welcome members of the public who are here today as well. And as Dr. Overturf had introduced the topic for today, a discussion of the ALVAC plus AIDSVAX vaccine regimen, these are preventative HIV vaccines that are based on Clade E.

You'll be hearing more in detail a discussion of the trial to be presented by the sponsor, but just as a very brief introduction, ALVAC is a canarypox-vectored vaccine that can be considered the prime in this vaccine regimen. The AIDSVAX B/E is a gp 120 protein vaccine that can be considered the boost in this regimen.

Both of these vaccines contain epitopes of HIV that are meant to illicit a specific immune response against Clade E, which is the specific clade that circulates widely in Thailand, and that clade has been recharacterized as a circulating recombinant

form.

You have all been reading about this trial in the lay press as well as in journals. For example, a recent series of articles in the journal *Science* had aired these differences in the scientific merit of the study. However, the purpose of today's VRBPAC is not to discuss these differing scientific opinions but to present to the Advisory Committee an update on the ongoing study, in particular, the decision to allow the trial to proceed under U.S. IND.

In addition, we wanted to introduce you to some of our regulatory challenges that we're going to be faced with, in particular with this trial. One of the regulatory challenges that we'll be faced with has to do with the complicated genetic diversity of HIV. HIV can be defined as clades or subtypes, and that definition is based on differences in the short sequences of the outer most portion of HIV, the envelope protein.

In addition to clades that have been identified, new circulating recombinants have been recently identified. And to further complicate the

genetic diversity, formerly recognized clades have been recharacterized as circulating recombinant forms. And in this particular case, Clade E has been recharacterized as a circulating recombinant form.

HIV's genetic diversity does represent a potential obstacle in the development of an HIV vaccine. A recent article in the *New England Journal of Medicine* had described an individual with a well-characterized clade of HIV who experienced a new acute retroviral syndrome associated with a low CD4 cell count and an increasing HIV RNA that was due to a different clade HIV. In addition, numerous other articles have described this phenomenon of super infection.

So it calls into question how broad do immunological responses have to be and how much cross-clade recognition does there have to be with an HIV vaccine? One current thought is it perhaps is necessary to illicit an immune response against the outer most portion of HIV, the envelope protein. And as a consequence, much of HIV vaccine development today is clade-specific.

This slide is meant to again represent the complicated global diversity of HIV. You can see that Subtype B is the predominant subtype that circulates in North America, Europe and Australia. This slide also highlights the very complicated genetic diversity in Subsaharran Africa. But I wanted to call your attention to Southeast Asia and Thailand where Clade E, or what is now recognized as a circulating recombinant form, is the predominant subtype that circulates in Thailand.

Dr. Jesse Goodman has taken some of our internal discussion regarding our regulatory challenges in the field of HIV vaccine development and has presented our internal discussion in a public forum, and I wanted to share with you a slide that he had presented at a recent conference, at the International Conference of Drug Regulatory Authorities that occurred earlier this year.

And in Dr. Goodman's slide he had posed the following interesting issues in HIV vaccine development. And he had asked a rhetorical question: Is U.S. approval possible for an HIV vaccine that

incorporates only non-U.S.-prevalent clades? And this particular question, if you will, or this particular point applies directly to today's discussion.

Dr. Goodman's second bullet point actually raises many issues, but the main point that I wanted to make from Dr. Goodman's second bullet point is a vaccine that has been demonstrated to have efficacy against Clade E, how would we view that as a U.S. regulatory agency where we might consider that to be a vaccine, a very limited efficacy for the U.S. population? And so that is the type of discussion that Dr. Goodman has at least presented to the public, and the slide, I think, serves as an introduction that these are regulatory issues that we'll be faced with in the future.

I wanted to emphasize that this is simply Dr. Goodman's slide. These are not questions that we're posing to the Advisory Committee today. This slide was simply meant to highlight some of our regulatory concerns that we'll be faced with.

So that concludes my introductory comments, and I wanted to turn the podium over to

Colonel Brown, who will be leading the discussion of the sponsor's presentation.

COL. BROWN: Thank you, Dr. Toerner, Mr. Chairman, committee members. This morning, we'd like to present to you an update on this trial, and we'll have three speakers presenting. In addition to myself, who will give you background information and information on the Phase II study, Professor Prasert is here with us from the National AIDS Commission of Thailand and will provide a perspective from that organization, and Dr. Supachai, the principal investigator of the Phase III trial is also with us, and he will give the actual description of the study design and current status.

The collaboration that was the basis of this trial goes back a long way. There's a U.S.-Thai Army collaboration in Thailand that's more than 40 years old, which has been studying tropical infectious diseases and has been very involved in vaccine development. And since 1991, a new mission was added there to work toward a preventive HIV vaccine. And that was an agreement between our two military

organizations. That collaboration has expanded to include universities in Thailand and vaccine manufacturers and became more formalized with the creation of the Thai AIDS Vaccine Evaluation Group, called the TAVEG.

But in parallel with the growth and maturation of that collaboration, the Thai national authorities have been addressing their own HIV epidemic and in the early 90s developed a national plan for the control of HIV, and as part of that have a specific plan for HIV vaccine development, which was first published in 1993.

So what I'd like to do is now just present Professor Prasert, who is a member of the National AIDS Commission and Chairman of the Subcommittee for HIV Vaccines. And he will share a perspective from that independent national authority.

DR. PRASERT: Thank you, Art. What I would like to present to you is about Thailand involvement in HIV vaccine research and development. My presentation will include Thailand national plan for HIV/AIDS vaccine development. It will include the

government commitment, the technical and scientific review of protocols and research proposals and development of infrastructure and training.

The national plan of HIV/AIDS vaccine development and evaluation is development by Thai Ministry of Public Health and research scientists from various institutions in Thailand with collaboration with the Global Program on AIDS of WHO at the time. And this plan has been approved by the National AIDS Commission and launched in 1993, placing HIV vaccine research and development on a fast track. The publication on that is in a Thai version and English version.

The national plan aimed at research and development of safe, effective, affordable and accessible HIV vaccine for the Thai people at the earliest possible date. The main objective of the national plan on HIV/AIDS vaccine are to develop a comprehensive, well-coordinated, long-term strategy for the evaluation of the safety, immunogenicity and efficacy of preventive, therapeutic and at the time we also forecast on perinatal HIV/AIDS vaccine in

Thailand, but now it's a low priority now, and to develop and explain the policy and procedure for planning, implementation, oversight, administration and evaluation of HIV/AIDS vaccine related with those activities in Thailand, and to facilitate the conduct of scientifically and ethically appropriate HIV/AIDS vaccine trial in Thailand.

The infrastructure and research activity that we plan and have been done in Thailand are to establish virological and immunological HIV expertise, especially the HIV isolation in Thailand and characterization of clades and to strengthen critical at laboratory facility for Phase I, II and III trial; to develop epidemiological and intervention research studies required for cohort development for clinical trial and to conduct the social and behavior research of the volunteers and communities; to establish the appropriate data that has not existed in my country and we developed this up to international standard and to develop the National Specimen Repository that we have established before also.

This is the commitment of the government

and support from the government. The National AIDS Commission is appointed by the cabinet. This Commission is Chaired by the Prime Minister of Thailand. And under this umbrella we have several subcommittees appointed by the National AIDS Commission. And the Subcommittee on HIV/AIDS Vaccine Development is one among them. And the AIDS Commission appointed the Department of Disease Control, Ministry of Public Health to be the focal point to coordinate all of this, but all of these are independent organizations.

The National AIDS Commission established the Subcommittee on HIV/AIDS Vaccine Development and report back to this independent organization. And they collect information on HIV/AIDS vaccine development to the AIDS Vaccine Coordinating Unit of the Ministry of Public Health, and they also collect information from IRBs, and we have some coordination with the Ministry of Public Health, but it is an independent body.

The Subcommittee on Vaccine Development is to identify and prioritize research activities related

on HIV/AIDS vaccine evaluation, to provide coordination to all HIV/AIDS vaccine-related activities in Thailand and to provide scientific and technical review of all HIV/AIDS vaccine-related research protocol and proposals. This is the process we have done in the past and are going now.

The proposal and protocol must be submitted to the Subcommittee of HIV/AIDS Vaccine Development and Review for technical value before the research can be implemented. And the Subcommittee ensures that vaccine protocol meets appropriate regulatory requirements of Thailand and international. Upon the request of the Ministry of Public Health the research proposal and protocol would also be reviewed by WHO/UNAIDS Steering Committee on Vaccine Development and by independent review group in Thailand and when applicable by other funding agencies and investigator's host institution.

From 1994 to last year, we have reviewed and approved from Phase I, Phase II and III research proposal on HIV vaccine clinical trial to get a number and among them who are Phase III clinical trial.

In summary, I would like to present the national plan for HIV/AIDS vaccine, established in 1993, has led to the development of appropriate global research, infrastructure and training in various fields. We have independent scientific and technical reviews and selection of appropriate vaccine candidates and research proposal and the Subcommittee has sustained the government support and commitment. Thank you very much.

COL. BROWN: Now I'd like to continue with background for the Committee and then describe the Phase II trial and the process for advancement to Phase III.

The focus of the collaborative research effort has been to work in a multidisciplinary way but always focused toward the goal of preventive vaccine. So there's been work in virology, diagnostics, epidemiology, preventive education and the disease course of HIV in this population. Consistent with the national plan for vaccine development, there's been a large emphasis on development of infrastructure, both human and physical and capacity-building.

The candidate vaccines developed have benefited from the industry partners tailoring these vaccines to the local strains of HIV, which is predominantly E, as you've heard, but also B is there. And the vaccines, as you'll see, contain components of both these subtypes. The TAVEG itself has tested four of these candidates that have been shaped for the viruses in Thailand in a series of Phase I and II trials that have included more than 700 subjects.

The Phase II trial that I'll describe here, which was just published last month, was led by two principal investigators, Dr. Ponnee and Dr. Supachai who are here today. The Phase II was a double-blind, placebo-control trial. The vaccine candidates were modifications of vaccines that had been made with strictly Clade B products so that the ALVAC product now has E envelope but still had the B Gag-protease. The AIDSVAX product is a bivalent B/E with two antigens, monomeric gp 120s.

The immunization regimen was to give the prime, which is the ALVAC, at four time periods over a six-month period and then give the AIDSVAX as the

boost at the last two immunization visits. There were three study groups: A placebo group and a group that got a low dose of the booster vaccine and a group that got a high dose of the booster vaccine. The subjects in the trial were healthy adult Thais who have non-reactive results in commercial HIV EIA assays.

One hundred and thirty-three subjects were enrolled into this trial and 122 were vaccinated. In terms of safety and tolerability, there were no vaccine-related serious adverse events. Reactogenicity assessments revealed no severe local or systemic reactions. The false positivity that can be vaccine-induced was monitored, and at the peak time point, two weeks after the last vaccination, there were 60 percent of volunteers who had reactivity in a commercial EIA. Only two percent of those people met the criteria of positivity in Western blot. And the actual testing algorithm includes nucleic acid testing, and none of these people had positive nucleic acid tests, and all were shown to be false positives. There were no intercurrent HIV infections in this group during the study.

Humoral antibody responses are summarized on this table. The humoral arm of the immune system has been monitored with three assays: A binding antibody assay against both gp 120 B and gp 120 E, neutralization assays that have been set up against matched viruses of B and E Clade and an antibody-dependent cytotoxicity assay, also against target cells labeled with B and E gp 120.

The antibody responses, the seroconversions and the magnitude of responses, were greater in the group with the high-dose boost, and that was then selected as the combination to move forward to Phase III. The results in that group, you can see here, for binding antibody range from 96 to 100 percent, with the two antigens. Neutralization ranged from 71 to 98 percent. And antibody-dependent cytotoxicity ranged from 78 to 93 percent.

The cellular arm of the immune system was monitored in two ways: To look at both CD8 reactivity and CD4 reactivity. The HIV-specific CD8 CTL activity was assessed using the traditional chromium-release cytolytic assay. Detection of vaccine-induced

activity in this assay was detected as early as after the second vaccination and was still being detected for the first time in volunteers at the last study visit, which was six months after the last vaccination. The cumulative frequency was 23 percent, and cross-clade reactivity was documented. The placebo group was consistently found to be non-reactive in this assay.

CD4 cell function was assessed using a lymphoproliferation assay to the two envelope antigens, gp 120 E and gp 120 B, and the responses of vaccinees were just about 60 percent, as you can see in this table.

So in moving forward to Phase III, there were a number of factors that were considered. The program made decisions regarding vaccine candidates that, one, they should induce both arms of the immune system and that the cellular responses should include both CD4 and CD 8 responses. And, two, that the candidate vaccines should match as well as possible the circulating strains of HIV found in the region under study.

The vaccines themselves when tested had to be found safe and well tolerated. The immunogenicity needed to be comparable to that seen with the similar candidates that had already been developed with Clade B constructs and tested more extensively in the U.S. and Europe. And equally important is a requirement that there had to be a potential cohort which was well characterized and included information on HIV incidence and follow-up rates.

So when Phase II studies were ended, the various partners reviewed the information available and a joint agreement was reached among the U.S. and Thai government partners, the academic and manufacturing partners. A protocol was developed, which has been a long process. The final protocol was actually reviewed by ten different institutional and regulatory bodies.

The plans for this trial have been presented to a number of advisory committees. They within Thailand have been presented to the National AIDS Commission and its subcommittee. Within the U.S., it was presented to what was formally called the

Baltimore Committee. Internationally, this was presented to UNAIDS, and the plans have been presented at multiple meetings, including national AIDS meetings in Thailand for both AIDS, in general, and AIDS vaccines and the International AIDS Congress in Barcelona where there was an announcement by the partners that this would move forward.

The sponsorship of this Phase III trial is shared by both the U.S. Army Office of the Surgeon General and the Division of AIDS at NIH. The Army is the IND holder for this vaccine combination. The executing authority for the trial is the Thai Ministry of Public Health. The principal investigator is Dr. Supachai, and there have been multiple collaborators -- there are multiple collaborators that are essential to the successful completion of this large effort.

So, in summary, this Phase III trial is founded upon more than a decade of preparedness and capacity building, the support of scientific and clinical data and a unique partnership among academic, governments and industry.

So I'd like to now -- or we would like to

now shift and I'd like to present Dr. Supachai Rerks-Ngarm, who's a Senior Expert in Preventive Medicine for the Ministry of Public Health of Thailand and the principal investigator for this trial.

DR. SUPACHAI: Good morning, Mr. Chairman, the committee members, ladies and gentlemen. I would like to present to you the study design of the ongoing Phase III trial and the current status.

Our collaborative study has a primary objective to determine whether immunization with ALVAC HIV vCP 1521 boosted by AIDSVAX B/E gp 120 protects Thai volunteers from HIV infection. And we also have the secondary objectives to determine the effect of immunization on viral load and CD4 count after intercurrent infection. Also, we'd like to confirm the safety of this vaccine combination. The last secondary objective is to evaluate whether a patient in this combined vaccine trial is associated with behavioral change that increasing risk of HIV infection.

Our study design has a community-based, double-blind, placebo-control with a vaccine to

placebo ratio of one to one. The vaccine schedule is similar to what Colonel Brown has described as the Phase II trial in Thailand, which is the ALVAC HIV vCP 1521 at week 0, week 4, week 12 and week 24, then boost by AIDSVAX B/E at week 12 and week 24. It was especially slow serology negative and it's 20 and 30 years old. Each individual volunteer will be followed for three years post-vaccination.

This study designed based on the incidents of HIV infection in that locality of 0.34 per 100 person-years, which is lower of 90 percent comes in interval of the incidence found in the cohort study. We allowed the lost to follow up about five percent for six months and we target to enroll about 16,000 volunteers. With a conservative assumption, we would have about 90 percent power to detect difference between the vaccine and possible if efficacy is 50 percent of regular.

Every female volunteer will be tested for pregnancy before the vaccination. If found positive, the vaccination will be stopped and the outcome will be follow-up until the female volunteer gives birth.

The reactogenicity will be evaluated for 72 hours after the vaccination. For the adverse event, it will be assessed and provide risk reduction education at the vaccine and follow-up visits. And the behavioral risks will also be assessed at baseline and every six months.

The serology will be tested during screening at week 24 and then every six months with the standard pre- and post-test counseling. The plasma will be collected and stored at baseline and every six months the PBMC also at baseline six, 12 and 42 months. We will utilize our local health centers to enhance follow-up of each individual volunteer during the post-immunization phase.

This is a map of Thailand. Our study area located in eastern part of the country, which covers two provinces, Chon Buri and Rayong, and in each province we have a study area in four districts -- four in Chon Buri and four in Rayong. We used the government facilities in this trial. This is a picture taken from one of the health centers that served as the screening sites. All together we have

47 screening sites. Among the 47 screening sites, we have 40 health centers and seven district hospitals. In each screening site, we have two counselors. In total, we have about 100 counselors. And this is also the picture taken from the district hospital. We're involved with even district hospitals, and in one district we don't have district hospital, so we worked with the city clinic to serve as a clinical site. So all together we have eight clinical sites.

In each clinical site, we have ten counselors, two nurse coordinators, two site physicians, five clinical research coordinators, two pharmacy nurses and three research assistants. So all together we have about 200 personnel. All together we have about 300 to 400 personnel working for this trial, which has been carefully selected, and they all have been trained in advance before the trial has been initiated. They were trained for the GCP, for the counseling, for the protocol and SOP and especially trained among the medical site physician and nurse on the advanced cardiac life support.

This is a picture taken from one of our

government facilities. It belongs to one of the departments in my ministry that have been used as a trial registry and repository center. These individuals prepare, process the specimens taken from the field site to be ready to send to the lab in Bangkok. All specimens will be here. The cap really is to keep more than 600,000 specimens here.

This is a picture taken inside the core room, which belongs to my department, the Department of Disease Control, to distribute the EPI vaccine in the routine service. We use this as a vaccine distribution center. It's located in Chon Buri. In addition to these facilities I have presented to you, we also -- in addition to that, we also use another two facilities which belong to the government as well. One is the critical, the surgical lab at the Thai Army, which is involved with the Thai technician and American technician working there. That lab has been activated by the American College of Pathology. And another facility is the data management unit, which is located in the faculty of Department of Medicine, which belongs to the Mahidol University to manage all

the data in the field that has been faxed to that unit.

After training our personnel in all the facilities and refreshing them, we can initiate our trial on September 29, last year. And the first volunteer was vaccinated on the 20th of October, last year. We x-ray'd our site by using the facility of site-by-site initiations, and we can have all sites enrolling in February this year.

As of last week, we have almost about 10,000 volunteers screened, and about almost 6,000 volunteers has been vaccinated. So, by average, right now we have about 200 volunteers per week. This is the slide showing you the demographic data of our participants. We have recruited both male and female with slightly more male, and they come from both provinces, even from here, they come from other areas. But all of them moving in these two provinces to work and they plan to live here for longer than three years.

In terms of educational level, more than 60 percent they finish high school or higher than

that. In terms of occupation among our volunteers, this represented participation in this area. For the motivation to join this study, more than 80 percent of our volunteers they said that they would like to do good to society. And another thing you may notice that our volunteers can provide more than one answer to the questionnaire.

In terms of citing the study, we have the Pharmacovigilance Committee to look for the 30 of the volunteers that they will meet regularly, and we also have the external monitor, which conducted the monitoring against the TCP by our contractual research organization, and we also have the Data and Safety Monitoring Board, which is Chaired by Dr. Walter Dowdle, which includes international membership. The meeting is planned for every six months. The last meeting was in July, this year.

From that meeting, the Data and Safety Monitoring Board has commended our team on the professional conduct of trial, and no safety concerns identified. They advise us to monitor the element very carefully and recommended the trial to be

continued. Thank you very much.

CHAIRMAN OVERTURF: At this time, I can open the floor to the Committee for any questions requiring clarification. Yes?

DR. MARKOVITZ: I wanted to ask several questions about the data that you showed concerning the serological response to the vaccine. The first one, do I understand correctly that the 23 percent CTL response that's over a period of time, so if somebody had a positive CTL response at any time that it was measured, that's included in the 23 percent; is that correct?

COL. BROWN: Yes, that's correct.

DR. MARKOVITZ: And what percent had positive CTL at the end of this study?

COL. BROWN: I think at a single time point it was five to eight percent.

DR. MARKOVITZ: So pretty low then. Another question I have -- so for me I'm not sure that that's really an accurate way to present the data, because if you just have a positive one time, that's not really showing, I think, in my mind, CTL efficacy

of any sort of lasting variety.

The other point I want to raise, it's very clear when you read the paper in JID, and you presented the same data, about neutralizing antibody, I think for the uninitiated that's not really very -- you must include caveats with that. First of all, the 71 percent neutralizing antibody with Clade E, that's for either one of two strains. That's not both strains being neutralized. And, second of all, both of those strains, as you know, are lab-adapted, and it should be pointed out, I think, when you present that sort of data that at least the feeling in the AIDS research world is that lab-adapted does not count. What counts are primary isolates. So I think it's very important to point that out.

I had one other question, and then I'll ask you to respond. The other question is just -- I don't have a point of view on this next question, which is why are only two percent of the Western blots positive? I'm just mystified about that. I don't know if that's bad or good or anything, but it's surprising.

COL. BROWN: Because most of the reactivity was against envelope products.

DR. MARKOVITZ: Oh, I see. So it's negative in the sense that you would see the envelope in the Western but you wouldn't see other things?

COL. BROWN: The frequency of indeterminant Western blots is higher.

DR. MARKOVITZ: Higher. Oh, I see.

COL. BROWN: But to meet a criteria of positivity was just two percent.

DR. MARKOVITZ: I see. That makes sense. What about the situation of the neutralizing antibodies? I might add, do you have any data yet about neutralizing primary isolates? You must be looking at that in the lab at some point.

COL. BROWN: Let me ask one of my colleagues, if Dr. Kim might talk about the actual assays utilized here.

DR. KIM: As I understand it, the question had to do with the 23 percent cumulative CTL rate. That's a standard mechanism for reporting of CTL rates that are consistent with other trials done by the HIV

Vaccine Trials Network and its predecessor, the AIDS Vaccine Evaluation Group. At a single time point -- and we should point out that not only were there positives throughout the study but there are positives that continue after two or three years, and there may be people who are positive at two years who were not necessarily positive during the study. I think it speaks to the fact that the traditional chromium-release CTL assay may be at its limit of detection for CTL and that CTL may be present. In fact, of the people in the study, 90 percent had CTL on at least two time points.

To address the question about --

DR. MARKOVITZ: I'm sorry, how could that be, that 90 percent had it at two points? But wouldn't that have been included? I thought the 23 percent was if you had a positive --

DR. KIM: At any time.

DR. MARKOVITZ: -- result at any time.

DR. KIM: Right.

DR. MARKOVITZ: Oh, you mean 90 percent of the 23?

DR. KIM: Yes.

DR. MARKOVITZ: Oh, I see. I'm sorry.

DR. KIM: And then with regard to the T-cell line adaptation of isolates, while it is true that the CM244 isolate was, or is, lab-adapted, it was in fact -- CM244, and the reason it's selected, was that it is a primary isolate. And so adapting a primary isolate to grow in a standard CXCR4 positive cell line would be a rather difficult thing. So what we did was we created a cell line that expressed CCR5 and CXCR4 and adapted the virus to grow in that specially adapted cell line. What we do know is that this cell line -- that these viruses still require CCR5 in order to enter, so that although they are T-cell line adapted, they retain many of the characteristics of traditional CCR5-tropic viruses and that CCR5 is still required as opposed to a standard T-cell adapted CXCR4-tropic virus.

The neutralizing antibody data that you requested on primary isolates has been done on some of the isolates, and using a PBMC-derived assay, we were not able to detect significant quantities. Now, we

have to also recognize a primary isolate neutralizing antibody in a PBMC-based assay. However, we should point out that as a correlate of protection -- that there is no established neutralization correlate of protection and so that the mere absence of detectable antibody is of unknown significance at this point.

DR. MARKOVITZ: We have consensus over here. We'd still rather have it than not, however.

CHAIRMAN OVERTURF: Are there other questions?

I'd like to ask one question. You mentioned what the motivation was for entering the trial, but I wondered if somebody could explain a little bit what kind of information is given out in terms of an informed consent kind of involvement?

DR. PONNEE: For the informed consent process, to ensure that all participants really understood the trial before enrolled, they understand their role, their right to participate and also it's voluntary. We use various educational tools, for example, videos. We have two sets of videos, booklets, leaflets. And also, after watching videos,

we will have group discussion and individual discussion. And before signing consent form, they have to pass comprehension test before signing the consent form. And in the consent form, we make sure that they really know the risks and benefits and also freely have a choice to participate or not participate.

CHAIRMAN OVERTURF: I guess I was kind of concerned about how much of the science is explained. I assume that if they understand risks and benefits, part of the risk must be involved in explaining some of the limited science in lay terms.

DR. PONNEE: Yes. In there, there is an explanation of what's a vaccine and what's the preparation of the vaccine.

CHAIRMAN OVERTURF: Dr. Royal?

DR. ROYAL: With the analyses that have been done to date, have you see any trends with respect to behavioral changes that might be occurring in the vaccine recipients?

DR. SUPACHAI: In terms of the analysis, we plan to do it next six months, because we have the

baseline information, and then after six months we collect another data and analyzing trend.

With your permission, I would like to add more information concerning the information for the volunteer. Actually, it's a process of education. We have the educational activity for the community before they come to the site. In that educational activity, we include both the education information and the information about our trial in both discussion session and role play activities. And when they come to our site, they will get more information by watching the DVD that will illustrate everything about the trial, explain to them clearly what is going to be, what the vaccine means and what will be treated by our team. And, as Dr. Ponnee said, they have to pass a comprehensive test of understanding before joining the vaccine study. Thank you, sir.

CHAIRMAN OVERTURF: Were there other questions? Yes, Dr. McInnes?

DR. McINNES: I wonder if -- I'm still trying to get a handle on the immunogenicity profile of the candidates, vaccines and the regimen. And I

wondered if you would perhaps indulge me and go back to your slide on the antibody responses that showed the binding antibody, the neutralizing antibody and the ADCC. I'm still trying to understand your binding assay and your selection of concentration in your protein.

COL. BROWN: This slide?

DR. McINNES: Yes. Would you mind just going through this a little more slowly?

COL. BROWN: Well, again, if we're going to do methodology, why don't I let Dr. Kim do this? He's actually one of the people that carried out some of this work.

DR. KIM: I'm sorry, the binding antibody assay actually reflects a titer compared to an OD control or blank. So, in this case, protein is bound to a plastic plate and a standard ELISA is done. And so these are looking at a comparison of pre-to-post and also a blank control to establish the baseline OD, and then positive responses are considered things above that baseline.

For neutralizing antibody, all these

samples compare pre-immune serum to post-immune serum and are looking for a 50 percent reduction in P24 production as a result of exposure of the cells and virus to the serum, comparing pre-serum to post-serum. So anyone with greater than 50 percent reduction pre-to-post was considered our responder.

DR. FARLEY: Can I ask a follow up to that -- Monica Farley. Is there a threshold for the ELISA-binding antibody or is it just anything, any positivity? There's no defined threshold for what's a significant level?

DR. KIM: Typically, the binding antibody assays are greater than one to 100 titer.

CHAIRMAN OVERTURF: I'm sorry, I didn't hear what you said completely. Dr. Kim? Just speak a little more loudly.

DR. KIM: I'm sorry. The threshold for positivity was one to 100, but, typically, titers were far in excess of that. So a positive result is greater than one to 100. and so what you're seeing are percent responders. So a person is a responder if they have a titer greater than one to 100, realizing

that the average titer is higher than that, and many are in the thousands.

CHAIRMAN OVERTURF: Yes, Dr. Markovitz?

DR. MARKOVITZ: Yes. Jerry, don't sit down yet. I have a question, a follow-up question. I was ruminating on your answer here about the neutralizing antibody being of unknown significance. There are plenty of studies of monoclonal antibodies that neutralize HIV that look like they're protective. So while I think that it's clear that there's no absolute correlate of immunity for vaccine development, it does seem like -- from what I've been able to garner, and I believe that the feeling in the field is that neutralizing antibodies are actually important predictors. Of course, nobody really knows but that's the feeling. How would you respond to that, please?

DR. KIM: Absolutely. I think as a person whose lab does neutralizing antibody, I also feel very strongly that neutralizing antibody will be important. I think that one of the points that we need to recognize is that there was an experiment done where

you could -- Dr. Mal Martin and Riri Shibata had done an experiment where it was possible to transfer serum and protect against other strains.

I think that the only point that we want to make with regard to T-cell adapted strains is although the feeling is that they don't protect, we haven't formally demonstrated. The study does have the power to detect or to study this as an immune correlative protection, and I think that one of the important scientific pieces of information that we would like to get out of this study in a model of challenge that is purely human, rather than in a monkey where even under best of circumstances you get 100 percent of really the vaginal SIV challenge. You're aiming for 100 percent infection of all the monkeys. That is not an appropriate challenge, and so we have to realize the constraints of the models as well.

CHAIRMAN OVERTURF: Dr. Karron?

DR. KARRON: Yes. I was wondering if anyone could comment on the decision not to include an ALVAC-only arm in this trial?

COL. BROWN: I can give you an initial response. Actually, we, early on, when the epidemic was going at a much higher rate in Thailand, we had envisioned a trial that would have multiple arms. It would have an antibody-alone arm, a CMI-alone arm and a combined arm. And many of the preparations for trial were going on during that period. But as the Thais have been successful in limiting or bringing under some control their own epidemic, the incidence rate has fallen, and the reality has been that we would have to settle to just one arm. And not knowing what the correlate of protection is, the programmatic decision was to put everything on our side that we could and chose to have -- that we should try to illicit both arms of the immune system.

CHAIRMAN OVERTURF: Dr. Whitley?

DR. WHITLEY: There's been some discussion, obviously, by advisors to the vaccine trial that Scott Hammer chaired not long ago that addressed two issues regarding the co-primary endpoints of the clinical trial, and they were, I think, considered fairly carefully by that group of

people, suggesting that the total sample size of the population be decreased from 16,000 to 8,000 and that co-primary endpoints be identified.

By me simply doing the math for the clinical trial, if it's 200 volunteers a month who were being enrolled rather than screened, if I understand the slide correctly, it's still going to take you four to five years to complete the clinical trial, recognizing that you need to recruit 11,000 individuals from where you are at the present time, and you're going to accomplish that, it's at least four years, if not five years. You're only acquiring 2,400 patients a year. Two hundred times 12 is --

COL. BIRX: A week, 200 a week.

DR. WHITLEY: Okay. And they're entering the study a week. It begs the question then, you know, because there's been concerns about the design of the trial that have been alluded to in a variety of communities, is it not better to accept an enrollment rate of 8,000 with co-primaries to try and bring the clinical trial to the medical community as quickly as possible, recognizing that you have a Data Safety and

Monitoring Board and that Data Safety and Monitoring Board can help you monitor the incidence of disease and can be beneficial in deciding what the final sample size of the population should be. And I have to be a little careful because Dr. Self is here, and he was on that committee.

COL. BROWN: Let me try to divide that into at least two responses. On behalf of the military, our interest is in acquiring a vaccine that protects against infection acquisition. That's our primary objective. But I think the board you refer to, that working group is an advisory group to Dave's, and I'd like to ask Dr. Flores if he might comment on that interaction.

DR. FLORES: Thank you. My name is Jorge Flores. I am with the Division of AIDS of the NIH. We are, as you've seen in the slides, one of the partners or collaborators in this enterprise. It is true, the Division of AIDS asked the AIDS Vaccine Research Working Group that we established as a technical assessment group to comment on the potential for increasing the value of the study. And the

responses to that request they provided us -- included among then what you have mentioned, namely increasing the evaluation of viral load to make it a co-primary endpoint. And if that is the case, a corollary to that would be that if we are going to analyze viral load to primary endpoint, the sample size of the study could potentially be reduced.

The team, including all the partners, have agreed to the recommendation of the group, or the AIDS Research Advisory Committee, and are planning and have already moved towards elevating the analysis of viral load in this study to the primary analysis. But we'll certainly have a series of consequences -- and Dr. Self is here, maybe he would like to follow up as well -- has a series of consequences in the trial, of course, that there's an increased error rate that is produced just by analyzing both viral load and impact on acquisition together.

But in addition to that heat that is taken on the sample size by doing the combined analysis, there are several other reasons why the Division of AIDS and some of them, actually, were agreed upon by

our advisors. I feel that maintaining the sample size is important. Among them is the uncertainty the incidence that was originally planned for is maintained along the study. As you know, Thailand is one of the countries in the world that has most successfully controlled the epidemics. So we have some concern that if that incidence is not maintained, the study itself will suffer.

Another major consideration that we have and that has been discussed recently, especially at the endpoints meeting where many people in this room participated, was the need in the field to establish correlations between viral load as modulated by a vaccine and the potential clinical benefit that a drop in viral load may imply. That would require following up volunteers who become infected in a trial like this and there is a thorough plan to follow the volunteers of this trial who become infected. That would require also that the number of those volunteers be sufficient to again establish a viral load, a body surrogate marker for clinical progression.

CHAIRMAN OVERTURF: Are there further

questions from the Committee? Yes?

DR. MARKOVITZ: Well, we have to ask, so forgive me, but I'd really like to know in a succinct manner, obviously everybody in the world would love to see a successful HIV vaccine, and we're all -- whatever the genesis of this trial is, obviously it would be great if it's effective. But how do you respond to the strong feeling in sort of the HIV research community that the at least laboratory demonstration for efficacy is rather minimal with this approach? Why do you think this is going to work? I know you've been asked this by many people, but I'd just like -- our Committee I think has to hear first hand why you think this will work.

COL. BROWN: I think I'll ask our Program Director, Colonel Birx, to respond to that.

COL. BIRX: Fundamentally, we don't know if it's going to work, and that's why we've committed not only the funding but the human resources and the training and the infrastructure to ask the question in the best way and most comprehensive way possible and the most rigorous way so that we'll know at the end of

the trial does it work or not.

I think we are all struck by the change in the field over the last two years. The development of these highly new sensitivity assays that are highly sensitive for both cellular and humoral immunity that didn't compromise specificity, assays that are developed by Merck and by Dades, through the VRC and their HBTN Network. We're very excited about applying these new techniques to the samples that have already been previously stored so we can really understand when we're moving a vaccine forward, particularly one that was moved forward under a chromium-release full functional assays, how the ICS assays that rely on IL-2 or gamma-interferon relate.

So I think there's two aspects of your question. One is to do a thorough evaluation of these new highly sensitive immunologic techniques and see how this vaccine stacks up. We know from the LPA data that 60 percent produced IL-2s. So you can imagine in an ICS assay 60 percent are going to produce IL-2.

So we're very excited about looking retrospectively to understand this vaccine's

performance in a more comprehensive way, but we're also very interested in looking prospectively at both the parameters for efficacy and disease progression that will really add value to the field.

So I think this trial will answer a critical military question about acquisition, and I can't minimize that. When a soldier becomes positive, he's non-deployable. So a critical aspect is the acquisition. But we're also very interested in I think the way the Thais have demonstrated their commitment for the last decade. We're very interested in using this trial in any way possible to bring more information to the field, and I think this viral load and CD4 in the context of a health care delivery system that's rigorous and comprehensive will be able to track disease outcomes in all of these patients. And so that will add value to the field of really documenting the role of viral load and CD4 and disease outcome.

So I think there's tremendous value in the trial. Learning how to enroll women, learning how to maintain women on trials, I think that's been very

successful. And getting those lessons learned to our other sites in Africa will be critically important for the next efficacy trial that will have a different immunologic platform and a different profile. So we're excited this is one step forward, but we realize it's only one step, and there may be ten more or 20 more to come. Thank you.

DR. MARKOVITZ: Excuse me, what does ICS stand for? I don't know that terminology.

COL. BIRX: Those are intercellular cytokine assays that are now being used, developed and studied, both CD4, CD4 memory, CD4 naive and CD4 long-term, functional and memory aspects.

CHAIRMAN OVERTURF: Any further questions? I think we're ready to go to the next agenda item, which is the open public hearing, so I'll turn the meeting briefly over to Christine Walsh.

MS. WALSH: 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.

CHAIRMAN OVERTURF: Again, I am required to read into the record the following: 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, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason -- we lost half the statement. For this reason, the 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 the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with the 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.

Our first speaker in the public open hearing period is Mr. Richard Jeffries, who represents the Treatment Action Group.

MR. JEFFRIES: Hi. Good morning. I appreciate the opportunity to speak briefly to the Committee. We've actually submitted written comments, so I won't send everyone to sleep by reading this verbatim but just try and touch on some of the main points.

I think to sort of get back to the question this morning about licensure, one concern for us is this huge trial, from what we understand, cannot provide data that would lead to licensure, even in Thailand. And I think just some of the controversy around the trial, I think, I'd argue, is to do with the way circumstances have changed around it. I think the issue of the single-arm design is really critical and that would have been partly addressed by the HVTN

201 study they included in ALVAC-only arm that got cancelled. And I think maybe one lesson for the future here from TAG's perspective is that we need to be able to get advice as circumstances around a trial change. So when those things happen, when the AIDSVAX trials fail to show efficacy, if there could have been consultation here and with the AIDS Vaccine Research Working Group, that might have actually helped kind of amend the trial and sort of keep it a little bit more relevant.

And I think if you're going to commit the kind of resources that are involved in this trial, you really need to get a clear answer. And if there is efficacy, which would obviously be great, we're not going to know the contribution of ALVAC versus the contribution of AIDSVAX or whether AIDSVAX even had a negative effect.

It was interesting to hear that the military's primary concern is acquisition. You know, I think that I hope that that's clear to the participants in this trial, that that's the question that's being answered. I think a lot of people have

cited altruism as their motivation for being a part of this trial. I hope they're aware that the focus on acquisition is really based on a priority of the military and not necessarily the Thai community.

I think I would like to acknowledge that a lot of people have put an incredible amount of work into this trial and it's incredibly easy to stand and critique it and incredibly difficult to make a vaccine efficacy trial happen, but I think we just reiterate the point that better consultation and more independent advice would have been really helpful.

The other thing we've done in our written comments is just given a brief outline of our understanding of the AIDS Vaccine Research Working Group recommendations, but I'd like to just be clear that that's our understanding. If people have additional questions about it, if we've made any errors, that's our responsibility. And I think maybe if there's another discussion at this Committee, it would be useful to have a formal presentation by someone from that group.

And I think just to conclude sort of our

perspective of the lessons for the future is that we really need to -- there's a lot of talk recently about improved collaboration in the HIV vaccine field. I think some better consensus around the parameters that justify moving forward with an efficacy trial would be really critical. I think it's kind of notable that the International AIDS Vaccine Initiative have just announced that they've decided not to go forward with a DNA/MVA vaccine because the immunogenicity for CTL was around, I think, between ten and 20 percent, which is pretty much what we've seen here with ALVAC, and yet we're doing this huge trial.

And, also, I think we'd encourage the FDA to take a closer look at the efficacy trial designs, because we want to keep our eyes on the prize. And what we want to have is a licensable HIV vaccine. We don't want to be doing efficacy trials that then require another efficacy trial before we actually get a licensable product. We need to have something out there to protect people. Thanks very much.

CHAIRMAN OVERTURF: Thank you, Mr. Jeffries. Is there anybody else who would like to

make a presentation during the open public hearing?

Well, then this will be the end of the open session. In 15 minutes, we will begin our closed session after the break. This session is closed to the public. We are asking the public to leave the room at this time and to take all their possessions. Any briefcases, suitcases or personal belongings left in the room will be placed outside the door before we begin our closed session.

The press, any media equipment that cannot be removed in the next 15 minutes must have the power turned off. When the closed session is over, you can then come and remove any remaining equipment.

So at this time, we are about ten minutes ahead of schedule, and we are scheduled to reconvene at 10:45. Thank you.

(Whereupon, at 10:23 a.m., the VRBPAC Open Session was concluded.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Vaccines and Related Biological Products Advisory Committee (Open Session)

Before: DHHS/FDA/CBER

Date: September 23, 2004

Place: Bethesda, Maryland

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.