DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE (AVAC) MEETING

Wednesday May 14, 2003

8:00 AM

Holiday Inn
Two Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

Roy M. Gulick, M.D., M.P.H., Chair
Tara P. Turner, Pharm.D., Executive Secretary

MEMBERS:

Courtney V. Fletcher, Pharm.D., Consumer Representative
Princy N. Kumar, M.D.
Wm. Christopher Mathews, M.D., M.S.P.H.
Sharilyn K. Stanley, M.D. (by phone)
Victor G. DeGruttola, Sc.D.
Janet A. Englund, M.D.
Kenneth E. Sherman, M.D., Ph.D.

CONSULTANTS (VOTING):

Douglas G. Fish, M.D.
Mary E. Guinan, M.D., Ph.D.
George J. Pazin, M.D., M.S.
Linda S. Potter, Dr.P.H.
Ronald G. Washburn, M.D.

GUEST SPEAKER (NON-VOTING):

H. Hunter Handsfield, M.D.

HHS FEDERAL GUEST (NON-VOTING):

Katherine M. Stone, M.D.

PATIENT REPRESENTATIVE (NON-VOTING):

Charles Ebel

FDA STAFF:

Debra Birnkrant, M.D.
Mark Goldberger, M.D.
Harry Haverkos, M.D.
Fraser Smith, Ph.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. GULICK: Good morning. I am Roy Gulick, from Cornell University in New York, and I am pleased to call to order this meeting of the Antiviral Drugs Advisory Committee today. We will start with introductions of the committee, and we will start on this side with Mr. Ebel. So, please state your name and your affiliation.

MR. EBEL: My name is Charles Ebel. I am employed by the American Social Health Association. I have worked in patient advocacy for genital herpes for about fifteen years.

DR. STONE: I am Katherine Stone. I am a medical epidemiologist in the Division of STD Prevention at the CDC, the Centers for Disease Control and Prevention.

DR. POTTER: Hi. Linda Potter, private consultant--

DR. GULICK: Sorry, turn the mike on.

DR. POTTER: There, now it is okay. My area of expertise is primarily compliance and adherence with regimens.

DR. GUINAN: I am Mary Guinan, from the Nevada Public Health Foundation in Carson City,

Nevada.

DR. PAZIN: George Pazin, formerly from University of Pittsburgh; now at the VA Hospital in Pittsburgh.

DR. FISH: I am Douglas Fish. I am the Division Head of HIV Medicine at Albany Medical College, in Albany, New York.

DR. WASHBURN: Ron Washburn, LSU and Shreveport VA.

DR. MATHEWS: Chris Mathews, University of California, San Diego.

DR. FLETCHER: Courtney Fletcher, University of Colorado Health Sciences Center.

DR. TURNER: Tara Turner, Executive Secretary for the committee.

DR. KUMAR: Princy Kumar, Georgetown University, Washington, D.C.

DR. SHERMAN: Ken Sherman, University of Cincinnati and Director of Hepatology and Professor of Medicine.

DR. DEGRUTTOLA: Victor DeGruttola, Harvard School of Public Health.

DR. ENGLUND: I am Janet Englund, pediatric infectious diseases, University of Washington.

DR. SMITH: Fraser Smith, Statistical Reviewer, FDA, CDER.

DR. HAVERKOS: Harry Haverkos, Medical Officer, FDA.

DR. BIRNKRANT: Debbie Birnkrant, Director of the Division of Antiviral Drug Products, FDA.

DR. GULICK: One committee member is joining us by teleconference. Dr. Stanley, can you hear us?

DR. STANLEY: I can hear you loud and clear. Dr. Stanley, from Texas Department of Health, not in Oklahoma.

[Laughter]

DR. GULICK: We did wonder about that, Sharilyn.

DR. STANLEY: Unfortunately, there are ploys why I am here and not there, and I wish I were there.

DR. GULICK: Well, thanks for joining us by teleconference. Tara Turner will now read the conflict of interest statement.

Conflict of Interest Statement

DR. TURNER: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the

record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions:

Mr. Charles Ebel will be permitted to participate in the committee's discussion. He is, however, excluded from voting.

Dr. Princy Kumar has been granted a waiver under 21 U.S.C. 344(n)(4) for owning stock in the sponsor and competitor. The stock is valued from $5,001 to $25,000.

Dr. Roy Gulick has been granted a waiver under 18 U.S.C. 208(b)(3) for consulting to the sponsor on unrelated issues. He receives less than $10,000 a year.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building. The signed disclosure statements are available for public review at this

meeting.

With respect to FDA's invited guest speakers. there are reported interests that we believe should be made public to allow the participants to objectively evaluate their comments:

Dr. Hunter Handsfield would like to disclose the following interests in GlaxoSmithKline. His employer, the University of Washington, has received contract and/or grants from GlaxoSmithKline and he is an investigator on GlaxoSmithKline sponsored studies. He receives compensation for serving as a scientific advisor to Glaxo and speaking fees from agencies that received unrestricted educational grants from Glaxo.

Dr. Katherine Stone is an employee of the Centers for Disease Control. Dr. Stone is the first author on a scientific manuscript, with GlaxoSmithKline co-authors, on the results of a Glaxo acyclovir and valacyclovir pregnancy registry and she served on their advisory committee for the registry during 1984-1999.

Lastly, we would also like to note for the record that Dr. Eugene Sun is participating in this meeting as the acting industry representative,

acting on behalf of regulated industry. Dr. Sun is an employee of Abbott Laboratories.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. Thank you.

DR. GULICK: One clarification on that, Dr. Sun was unable to be here, on the committee, today. Dr. Katherine McComus, from the University of Maryland is going to take a minute to tell us about a side project that is going on today.

DR. MCCOMUS: Thank you and good morning. My name is Dr. Katherine McComus and I am at the University of Maryland. I am here today to ask your assistance in a survey that I am conducting with collaborators at the Food and Drug Administration to examine public attitudes and understanding of the conflict of interest

procedures that the FDA uses to manage and monitor real or potential conflicts of interest of its advisory committee members. People in the audience are being asked to complete this questionnaire and members of the advisory committee are also distributed a questionnaire under a separate cover. If you have a chance to complete it today--I realize it is a very busy day, but there is a box outside at the registration desk and you can drop it in there. Otherwise, there is a business reply envelope and you can mail it back to me later.

Your responses are anonymous. Your participation is voluntary but your participation is very important to the reliability and validity of this study. This study is being conducted across several centers at the FDA and at multiple advisory committee meetings. We would like as a high a response rate as possible so that we can accurately represent your opinions, provide feedback to the Food and Drug Administration and perhaps improve overall satisfaction with the advisory committee process.

I will be here today if you have any questions. Thank you again for your time. Thank you for the opportunity.

DR. GULICK: We were advised yesterday that informed consent is not required for this but that it has been approved by local IRBs.

We will now turn to Dr. Debra Birnkrant to make some opening remarks on behalf of the agency.

Opening Remarks

DR. BIRNKRANT: Good morning. I would like to welcome back our advisory committee members and extend a welcome to our guests and consultants this morning.

[Slide]

Today we will be discussing the supplemental new drug application 20550 for valacyclovir for the prevention of the transmission of genital herpes amongst monogamous heterosexual couples. We are bringing you this application today because we seek your input in this discussion, and this is the first time we are being requested to include wording in labeling "for prevention of sexually transmitted viral infection." We will also be asking you to comment on public health implications as well.

[Slide]

Although Dr. Hunter Handsfield will be presenting an overview of genital herpes this

morning, I wanted to start this morning off with a few comments related to management of herpes infections, and this is taken from the CDC STD treatment guidelines, published in the MMWR, May, 2002.

There are three key principles of management of genital herpes, consistent and correct use of condoms; counseling and chemotherapy with three approved antiviral drugs, one of which, valacyclovir, we will be focusing on today.

[Slide]

Valacyclovir is approved for first, recurrent and suppressive episodes of genital herpes. These regimens are actually taken from the CDC guidelines and are slightly different from the labeling of the product. In addition, we recently approved valacyclovir for suppressive therapy in HIV-infected subjects with CD4 counts greater than 100.

[Slide]

In addition to these indications, GlaxoSmithKline studied valacyclovir for the prevention of transmission of genital herpes amongst monogamous heterosexual couples in study HS2AB3009. This was a study in more than 1,400

discordant couples for genital herpes. This sample size was achieved after screening more than 4,000 discordant couples. It studied the dose of valacyclovir 500 mg daily for eight months. In this study, which you will hear much more about later this morning, condom use was encouraged and the primary endpoint was clinical signs or symptoms of genital herpes plus laboratory confirmation.

[Slide]

The issues we will be asking you to address this afternoon include the following: The appropriateness of the endpoint in the clinical trial and for future clinical trials, as well as the trial design; the applicability of the results to other populations, given the restricted patient population that was studied in this clinical trial; screening issues related to the fact that more than 4,000 couples had to be screened in order to achieve more than 1,400 couples to enter the clinical trial; an issue related to the high dropout rate in relation to the event rate in the clinical study--again, we will be asking you about the impact on public health guidelines and, as with all antiviral drugs, we will be asking a question about resistance issues with wider use of

valacyclovir.

[Slide]

An overview of the day is on this slide. As I mentioned, Dr. Hunter Handsfield will be giving opening remarks with regard to geital herpes. This will be followed by the GlaxoSmithKline presentation. Actually, we may delay clarifying questions until after the FDA presentation, which will be done by Drs. Harry Haverkos and Fraser Smith. Then there will be a time for questions and discussion. The open public hearing will be held this morning, before lunch. Following lunch we will have a charge to the committee and questions. Thank you very much.

DR. GULICK: Thanks, Dr. Birnkrant. We will turn now to our guest speaker, Dr. Hunter Handsfield, from the University of Washington.

Public Health Aspects of Genital Herpes

DR. HANDSFIELD: Good morning. Dr. Gulick and colleagues and interested persons, thank you very much for the invitation to participate in this. I have been looking forward to it with some enthusiasm. Thanks in particular, Harry Haverkos, an old friend from his days at the Division of STD Prevention at CDC, for those of you who are not

aware of his background in that arena.

In the further discussion of conflict of interest, it actually directly relates to why I am here today in a way. I spent my career in sexually transmitted diseases, more than a 20-year career in prevention, epidemiology and so on, predominantly in the bacterial section of transmitted diseases. I had the opportunity to take sabbatical leave at CDC in 1997 and 1998, and my sabbatical was largely supported financially by Glaxo Wellcome and SmithKline Beacham. My focus in that sabbatical was to really take the first steps with the Division of STD Prevention to look systematically at prevention aspects and public health issues concerning the viral STDs other than HIV and hepatitis, which is not directly the responsibility of the STD Division. That led me into essentially a year of delving into the public health aspects of genital herpes in particular.

My sabbatical was followed, as it happens perhaps as an indirect indicator of CDC's growing interest in viral STDs, by Dr. John Douglas who spent a similar year working mostly on human papilloma virus infections and, perhaps not insignificantly, Dr. Douglas has recently agreed to

assume the position of Director of the Division of STD Prevention, perhaps indirectly reflecting the level of interest of CDC in looking carefully at the public health aspects of viral STDs.

My task this morning I see as sort of to set the context of some thoughts about the epidemiology of this disease from a public health perspective. It is really a review and I hope there is not very much new to most of you. In fact, those of you on the committee who had the time and energy on the airplane flying in to read GlaxoSmithKline's overview in their application, the epidemiology data and so on is actually quite excellent and I thought quite objective, and an excellent summary and so much of what I have to say will highlight some points that are made there. It also allows me to gloss over some things because they are clear in that fashion.

[Slide]

A simplistic review--I hope everybody knows about the basic biology of these two viruses. With mucocutaneous infection, retrograde infection along sensory nerves, latent infection potential for recurrences--some of the terminology is evolving whether there are true biological

recurrences in terms of viral replication or some level of ongoing viral replication, things other than replication per se that influence transmission of virus down nerves, and recurrent mucocutaneous lesions is an issue that I think is still not totally settled and discussed by people who study this disease at a laboratory level.

We have two viruses, cleverly called types 1 and 2. Type 1, as you well know, mostly causes oral labial disease but does cause high proportions, depending on where you are in the world and what population, of initial genital herpes. HSV-2, by contrast, is really rare in the oral area. It is a very rare person walking around with oral so-called fever blisters that has HSV-2 infection. When oral HSV-2 occurs it is almost exclusively in either overtly immunodeficient persons, such as persons with overt AIDS as has recently been published in studies, or in the context of initial infection when infection was simultaneously acquired in the oral cavity and the genital area.

The corollary to that is that of recurrent genital herpes the vast majority is type 2 virus. If you are unlucky enough to get herpes but lucky

enough for it to be HSV-1, and I will show you data on this, you are far less likely to have recurrent outbreaks of disease and also less likely to have subclinical shedding of the virus with the potential for sexual transmission, at least by vaginal intercourse.

[Slide]

It is not a formally reportable disease. Indirect methods and sentinel surveillance is required to understand the frequency of this disease. This data set is from the National Disease and Therapeutic Index, over three decades, and it is initial visits to clinicians' offices because of genital herpes. The up and down is a sample size study design artifact. The upward trend is clear although, of course, these data don't let you distinguish between increasing incidence, increasing patient concern and increasing clinician acumen and diagnosis.

[Slide]

These data are in the information provided by the sponsor. They simply make the point that genital herpes is in the middle ground of the annual guesstimated--and I have to say guesstimated incidence of sexually transmitted diseases. They

suggest at the low end half a million; at the high end, in a recent analysis, 1.6 million new cases occurring per year in the U.S.

[Slide]

The prevalence of genital herpes, however, is highest of all STDs. That is because, as the cute saying in the STD world goes, "what is the difference between herpes and true love? Herpes is forever." Once you get herpes, it stays. So, the seropositivity is an accurate indication of people who are infected, are believed to remain infected and so as long as infection is occurring at a rate higher than the rate with which people with herpes are dying in the population, the disease accumulates. So, we are dealing with something like a quarter of the U.S. population infected with genital HSV-1 or 2.

[Slide]

I think everybody in the room is aware of the National Health and Nutrition Examination Surveys, previously done in discrete cycles called one, two and three. What is now sometimes being called cycle four is really what is hoped to be, by the Center, an ongoing population-based sample. NHANES is a population-based access to Americans

that includes extensive health questionnaires and also serum banking. The banked sera from these studies have been looked at for HSV-2 serology and they provide the core information now available on prevalence of this disease in the U.S.

What it shows is that from the cycle that had a mid point in 1978 to the cycle that had a mid point in 1991 there was a 25-30 percent increase in overall prevalence that occurred in both men and women. The other point to draw from this slide is that in every survey ever done, for practical purposes, the prevalence of infection is higher in women than in men and the incidence of infection when people are followed at risk is higher in women than in men, probably reflecting differences in anatomy in terms of the nature of the exposure or the nature of the surfaces exposed to the virus during intercourse.

[Slide]

Here is where we come with that number that I showed you on the pyramid. The NHANES II data were around 16 percent after adjustment for various issues in study design, believed to have increased to about 22 percent prevalence in 1991, which translated to 45 million people. The number

of persons infected since 1991 is a little bit conjectural but the estimate supports something in the range of 5-15 million, depending on which rates of new infection you focus on.

Some unknown number of the roughly 50 percent of the U.S. population as adults that are HSV-1 seropositive have genital as opposed to oral labial infection. It is impossible on a population basis to know that number very well so I put a double question mark here. I don't know whether it is two million, 10 million or 15 million but it is a lot. That is where you can come to the conclusion that something like a quarter to a third of the U.S. population likely is infected.

[Slide]

There tends to be, I find, in people who are not familiar with this disease and with sexually transmitted diseases in general a skepticism from time to time about whether that proportion of the population really acquires an STD. These tend to be looked at with some emotionality from a lot settings and the concept that many of us get it doesn't set well with some people psychologically, socially, politically and sometimes at the gut level. I will just make the

point that human papilloma virus infections is probably acquired by 70 or 80 percent of us but within our first two to four lifetime sexual partners so that is even a more normative event to acquire HPV.

But that having been said, what these data show is the seroprevalence in the NHANES I study of SHV in whites by age. I show the '78 data because the 1991 data were not analyzed below age 12 or 15 so we didn't have the data down here. What it shows is that whereas HSV-1 seroprevalence rises on a more or less linear basis as age increases, HSV-2 infections are essentially absent before the sexually active years and the acquisition rate obviously declines to very low levels after the sexually active years. So, after someone reaches their late 30s they become, as has been used in the sexually transmitted disease epidemiology modeling world, sexually dead. So, all of the acquisitions are basically occurring in the sexually active years. So, that is just one piece among many of the evidence for those of you who might be skeptical that, yes, HSV-2 infections are sexually acquired.

[Slide]

Many of you have seen these data before and in a way, there is this almost too cute sort of slant to them, but I think they are important to take into account. This is one question on health-related random digit dialing survey, conducted by the American Social Health Association a few years ago, in which a number of health-related questions were asked. People were sought who were age 18-40. So, it is the younger half of the population.

This is simply one of many questions that was asked. It is listed verbatim here. I can read you a list of items--it is exactly the same approach used for political polling, the same sort of confidence intervals and so on. The sample size is around a thousand. I can read you a list of items that people may or may not consider traumatic. For each one, please tell me how traumatic it would be for you personally, "very," "somewhat," "not very traumatic," or "not traumatic at all." No surprise, people said getting HIV or AIDS would be very traumatic. The proportion saying it was very traumatic was virtually 100 percent. But two-thirds reported that they would consider it very traumatic if they acquired genital

herpes, and that was more than the proportion than rated it very traumatic to break up with a significant other, to get fired from a job or to fail a course in school.

Now, in a way that is crazy because this is a disease that, although it has its serious outcomes, the vast majority of infections are, in fact, mild. In fact, they are so mild that the majority of infections are entirely subclinical. Many of those can be converted into clinically recognized cases by proper counseling for people to recognize subtle symptoms. But it is probably not an accurate reflection of how bad the disease is, but it is a reflection of how people who recently acquired the disease or are afraid of getting it look at it.

[Slide]

This slide shows that although you may say, well, that is one data set but that makes the point of what about others? This is an entirely separate kind of data set that essentially comes to the same conclusion.

After 1997 the national STD hotline, conducted by American Social Health Association on behalf of CDC combined with the national AIDS

hotline, so it was a single hotline so the statistics are a little bit less easy to break out in this fashion since that time but the last year these data were available, 1997, if you limit the logged calls in terms of what they are about to disease specific calls, eliminating non-specific ones--what is an STD; do condoms work, etc.--and looking at disease-specific calls, herpes generated almost as many calls as all the rest of these combined.

HPV and warts was, in the middle 1990s, the most rapidly rising category so it wouldn't surprise me if more recent data would show these two running more closely to one another, and who knows which would be first, but the point is the viral STDs in general and genital herpes in particular generate far more concern than the traditional bacterial STDs on which I have spent the bulk of my professional career.

[Slide]

Clinical spectrum of disease--I hope this is also a review. First episode infection is divided into those who have true primary infection. These are people who have never been infected with either HSV-1 or HSV-2 and they tend to have the

clinically most severe disease. I say "tend" because most of these are subclinical. Even people who are HSV-2 seropositive and HSV-1 negative, which means when they acquired HSV-2, it had to be a primary infection--most of those or many of those, in fact, have no previous diagnosis or symptoms.

That said, among the people who development symptoms, these tend to be clinically the most severe. These are the folks who present with multiple bilateral lesions, systemic symptoms and so on, and a more prolonged course. Non-primary first episode infections are people who are infected typically with HSV-2 in the face of chronic, often undiagnosed and unaware HSV-1 infection, often acquired years before. These tend on average to be shifted toward a less severe clinical course and probably more subclinical infection.

Very important, many people present and already at the time of presentation have type specific antibody to the virus type that is causing the acute clinical syndrome, meaning that they have been infected for at least some weeks and, statistically, the vast majority have been infected

for months or years. That is, they are experiencing the first clinical outbreak in spite of an infection that was acquired some time previously. This phenomenon actually explains a large proportion of the magical transmission theories that we have all heard about--toilette seats, hot tubs and shared towels--because what it means is that people who show up with infection who are not currently sexually active or at risk for an STD because they are in a reliable monogamous setting and, of course, in that monogamous setting the other possibility is that transmission only just occurred in a relationship that had been going on for a substantial period of time. But in both cases clinicians tend to help patients reach for face-saving explanations that we now know simply don't occur. So, that is an important issue to understand from an epidemiology as well as a clinical management perspective.

Recurrent infection, of course, by definition is a second or subsequent recurrent outbreak that is clinically recognized, and most of the important information in understanding the epidemiology and clinical aspects of this disease in the past 15 years has been to understand that

subclinical infection overlaps all these categories and is subdivided into those who are truly asymptomatic and those who have unrecognized disease. Most are in this category. Data show that persons who are seropositive and unaware, and even who say they have had no symptoms, if counseled about even subtle genital symptoms to look for and then are given a green light to be seen clinically within a day or two as opposed to an appointment ten days later when symptoms appear, in fact, 60 percent or so appear with symptoms that are culture positive for herpes within about three months.

[Slide]

Much of these data, though not exclusively, I owe to my colleagues Anna Wald and Larry Corey who have made entire careers of studying this disease, and much of these data come from their facility. So, this is sort of the plenary study on the recurrence rate of 450-some persons followed for something over a year on average. Men had an average of five, women an average of four episodes in the next year of recurrences. I believe the true recurrence rate probably is the same in men and women. Carefully

counseled people in a herpes research clinic--men may be able to recognize subtle disease than women because of anatomical location and visibility. For a woman it is hard to know perhaps whether a labial itch is a lesion or not. Almost 40 percent had at least six recurrences in the next year and a sizeable minority had at least ten recurrences in the coming year.

I actually intended to bring a slide, and I guess I just forgot to include it in my slide set and it wasn't in my laptop, about the natural course over the years. The same data set has been looked at to look at recurrences and, actually, over the course of about eight years and beyond eight years the number of patients followed over time became too small to draw very many conclusions. But the average rate of decline was 0.7 to 0.8 recurrences per year.

The problem with those date is it is not linear, so people probably tend to have fairly frequent recurrences in the first year. There is probably usually then some decrement that goes on for many years. The same pattern appears to apply for subclinical shedding. So, we have fairly poor data both for subclinical shedding and for clinical

disease beyond eight to ten years. I think that is an important thing to keep in the back of our mind. It is true that we don't see very many people in STD clinics who are, for example, age 50 who say, "I got herpes at age 25 and here I am, 25 years later, still having two or three episodes per year." But the frequent recurrent rate and certainly the potential for transmission goes on, as ball park thinking, for at least a decade and what happens after that is harder to know. The recurrence rate is much lower for genital SHV-1.

[Slide]

This slide shows data on that. These were presented by Dr. Wald at IDSA a couple of years ago and have just been published, within the last month. The bottom line is when you follow HSV-1 infected persons for an average of 2.5 years, 40 percent almost had no recurrences that are clinically recognized; a third had only one; and only a quarter had four or more. So, it is very different than HSV-2 and the days to first recurrence are quite prolonged. As you can see, there is a decrement down to an average of less than one recurrence per year for many people after the first couple of years. So, the bottom line is

that people with this disease can be told with some assurance that they might have no recurrences though probably most people have one or two over the next year or two and maybe very little disease thereafter.

[Slide]

There is a lot of folklore about triggering recurrent outbreaks. It is interesting that for oral labial infection with HSV-1 the very fact of the name, cold sore or fever blister, reflects the role of intercurrent infections in stimulating outbreaks. We certainly know that sunburn or other actinic injuries can do it. Local trauma can do it. Ophthalmologists and ENT docs have learned that people with recurrent oral herpes often are being treated prophylactically with antiviral drugs at the time of surgery to prevent postoperative complications. Admittedly, I don't know the extent to which those procedures have been systematically documented as effective, but they are believed to be effective by many of those providers.

In contrast to folk lore, there aren't very many well documented triggers for HSV-2. The studies that are weak in this area but in general

those that have attempted to look at diaries of stressful events plus recurrent outbreaks and overlying objective psychological scoring methodologies have not been able to show much of a link between the things that patients often cite, such as stress, diet, menses and that sort of thing. I think it is important to remember the power of the human mind's capability of linking sequential events in a causal fashion, and I would ask anybody to contemplate whether it is herpes or myocardial infarction or a sprained ankle, whether they can look back and say, "oh, I haven't been stressed at all in the last week."

[Slide]

The biomedical complications--I stress biomedical because of the psychological complications I am going to talk about in a little bit--are a separate category, and I think everybody recognizes the predominant, frequent impact of this disease. It is psychosocial rather than purely biomedical although, obviously, they are interacting. But just to remind you of that spectrum, this is a protean disease that causes more than just the occasional genital sore. So, localized neuropathic manifestations, particularly

the first set of infection, bladder paralysis, sphincter incompetence and things like that; meningitis, either acute or recurrent. For those who don't know, the historic syndrome of what used to be called Molleret's meningitis or benign lymphocytic meningitis is, in fact, in at least 80-90 percent of cases recurrent HSV-2 infection of the central nervous system. HSV-2 as opposed to HSV-1 tends to cause meningitis. HSV-1 tends to cause encephalitis. There is a little bit of overlap but in an immunocompetent patients those distinctions hold fairly sharply.

Erythema multiforme, Stevens-Johnson syndrome--it is now known that recurrent erythema multiforme is in the vast majority of cases a complication of genital HSV-2 infection and preventing erythema multiforme in those cases is highly successful with suppressant antiviral therapy.

There is a range of perinatal and maternal morbidity, and Dr. Zane Brown is here and will undoubtedly address this if he has a chance to make some comments. The non-genital auto-inoculation syndromes, such as ocular infections and whitlow are an occasional issue, particularly the first

episode disease; chronic, localized disease, in AIDS patients; and I will talk a little bit more about the HIV transmission issue in just a minute.

[Slide]

In fact, here is the start of that theme. Dr. Wald and her colleague, Katie Link, did a masterful review and meta analysis of the literature, published a year ago in JID, and this is one figure from that paper. They found, I think it was, 20 or 30 studies that had looked at the association of HSV-2 infection with HIV prevalence or incidence, and within that there were nine studies that were either prospective cohort or nested control studies that had the opportunity to look at incident HIV infection as a function of preexisting HSV-2 antibody while also controlling for a variety of all of the things you would expect would influence it--sexual behavior, intercurrent STDs, and so on, and so on.

The results of those nine studies are illustrated here, and the overall meta-analytic conclusion was that there is, on average, about a two-fold increase of HIV infection, of incident HIV in the presence of HSV-2 antibody compared to the absence of HSV-2 antibody after controlling for a

number of sexual partners, frequency of sexual intercourse, use of condoms and other similar predictors.

[Slide]

These data are, to me, among the most dramatic. They are preliminary and remain that way. They come from the Rikai, Uganda study and I owe Larry Corey thanks for letting me use this slide which he, in turn, got from Mary Wawar and Tom Quinn and others.

I am privileged to be reviewing abstracts for the upcoming international society for SV research meeting that is occurring in Ottawa in July, and I have seen that these investigators have analyzed these data now with about double the number of couples reflected and, without betraying the confidence that is implicit in seeing pre-published work in that context, suffice it to say that it looks like these earlier results are not going to be undermined in any important way.

One hundred seventy-four HIV discordant monogamous couples, followed over time, looking at the HIV acquisition rate in those couples while those couples kept diaries of episodes of sexual intercourse, all these people lacked other risks

for HIV, other than their sexual cohabitation. What this looks at is the risk of HIV seroconversion according to the viral load, using a particular earlier assay that gave these particular numbers and looking at that by viral load in the HIV-infected persons per number of episodes of intercourse over time.

I think you can see obviously that if the HIV-exposed person, HIV negative exposed person was HSV-2 seropositive the risk of HIV transmission was dramatically higher than if that person was HSV negative. In fact, the transmission rate was statistically similar in a person who was sexually exposed to someone with a maximal viral load if the exposed person was HIV negative and in someone who was HSV-2 positive but exposed to someone with an undetectable HIV viral load by that assay. So, in this subset the importance of HSV-2 was a stronger predictor of HIV transmission than was HIV viral load.

[Slide]

So, I have concluded when I have spoken to practicing clinicians in the past couple of years that, other things being equal, HSV-2 infected persons have twice the chance of acquiring HIV on a

population basis. HSV-2 may be the post important STD. Not that the transmission efficiency for HIV is enhanced as much as it might be with, say, syphilis but HSV-2 is so much more prevalent in the population. The population attributable fraction likely is maximal for this particular disease.

Now, there is some controversy about when and how type-specific serological testing should be used as a screening tool in asymptomatic persons. My own feeling is that that debate unequivocally is over in people at high risk for HIV. We need to know of they are HSV-2 positive because it may help them understand that they are at double the risk of acquiring HIV if exposed. I think understanding this and its implications for the public health aspect may be at the pinnacle of what we need to be thinking about for this disease and prevention and, of course, control strategies for it which is, of course, at the core of why you are here today.

[Slide]

Subclinical shedding of this virus is extremely common. It is really unfair to try to summarize essentially your entire career in a single slide but here it goes. You can sort of summarize that it is present in people who test

themselves every day for weeks on end. It is present 1-10 percent of the days if you use PCR, up to 30 percent of asymptomatic days in people with symptomatic recurrent genital herpes. The maximum frequency, the group in the 5-10 percent of the days or 20-30 percent by PCR is in the first year after acquisition of this disease. It then declines. But it probably settles by culture in most people at the rate of roughly 2-3 percent of asymptomatic days by culture and roughly double that number of days by PCR for at least several years. The time course is probably similar to the clinical recurrence rate that we have already discussed. At least 95 percent of the people who are HSV-2 seropositive have some days when the virus is present in the absence of both detectable symptoms and things that even a trained observer can recognize as clinical disease.

Interestingly, the frequency is just as prevalent in people who are seropositive without history of clinical disease as it is in people with clinical disease who test themselves in between symptomatic outbreaks. Most episodes are symptomatic but unrecognized, although that is a little bit challenged by evolving data regarding

PCR because there are more people who are PCR positive and culture negative who truly don't have symptoms. This accounts for most transmissions. All STDs are transmitted selectively, like people whose clinical syndrome has shifted toward the subclinical end. It is sort of a no-brainer. People with painful genital sores, genital discharge, lower abdominal pain don't have intercourse as often as people without those symptoms. That is not exactly a surprising finding. It does underlie the importance of why active steps of partner notification are important for all STDs. Subclinical shedding is substantially reduced by suppressive antiviral therapy, both in terms of frequency of shedding and the amount of virus that can be detected and, as with clinical disease, it is uncommon with genital HSV-1 disease.

[Slide]

Psychosocial impact--I could spend the whole lecture on that. The fact that there is a psychosocial impact is at its core one of the reasons why we are all here today, at least some aspects of it. I would simply summarize specifically on the transmission issue because your

focus is going to be on what is the impact clinically, public health and psychologically on suppression of this disease with the goal of preventing transmission.

Every study of psychosocial impact or every survey of patients, and the quality of these studies is highly variable; the design is highly variable in terms of what they did and how they recruited patients or spontaneous respondents to web-based surveys, for example, are potentially highly biased. Nevertheless, there is great consistency.

Fear of transmission to partners is consistently among the top three. It is usually number one or two of the stated sources of concern, anxiety or stress by the patients. Then typically in these studies that particular issue--"I don't want to infect my partner and I'm afraid that I'll do it, and I don't know how to prevent that"--is typically cited by a third to 90 percent of the people participating in these surveys.

[Slide]

Just as a minor reflection, this is just a single web site. There are many out there. It is called Antopia, and I am not sure where the name

Antopia comes from but Antopia has a "dating service." MPwH I believe means matching partners with H, H meaning herpes or HPV. This is a quote from their web site yesterday, quoted to the point even of what is bold and what is colored in various ways. So, MPwH is a social resource and dating site for people with herpes and HPV. Right now it is May 13, 2003 and we have 36,000 registered members and 163 are currently logged in. Signing up is free; no obligation; your privacy and confidentiality are assured.

Simply, you don't have these sorts of things appearing--even if you make the argument that the people who participate in them are shifted towards those who are most concerned and not typical, you have to have lots of people to generate this sort of business.

[Slide]

I am not talking about therapy intentionally, except I do want to make the point that if you clinically suppress recurrent herpetic disease you have a significant impact to the good on psychological measures. This looked at herpes-related quality of life, 20 or so questions related to all the things that people with herpes

might be concerned about plus general questions about quality of life that weren't directly herpes related. Going higher means that over time you have an improvement in the score, that is, less psychological stress and improved quality of life. In five different regimens with different drugs in Dr. Patel's analysis for suppressant antiviral therapy compared to people on placebo there was a marked improvement in people who had clinical suppression of HSV compared to people who were on placebo, and over time, if you note, there is a general upward trend. The scores continued to improve with time. It was not a transient effect in people on antiviral therapy.

[Slide]

So, if people are so concerned about transmission, what are the data on transmission? Well, there are several studies out there. I am going to summarize only one because, (a) it is one I am the most familiar with and, (b) because it is probably the most comprehensively done one in a prospective fashion. It also served, I believe, as part of the genesis of sample size calculations for the study behind the sponsor's proposal today.

This was a retrospective--you know, the

Chiron vaccine studies have got to be the most successful scientific outcome of failed research. It generates all kinds of great analyses. The Chiron vaccine studies of HSV-2 serum negative persons enrolled monogamous partners of persons with herpes or STD clinic patients at high risk, 500-and some and almost 2000; followed them for 18 months with history, exams, HSV serologies, lesion cultures when lesions appeared; repeated safer sex counseling--we need to keep it in mind because these studies are shifted toward the null in terms of the likely transmission rates because of this need.

Outcome measures--primary measures HSV-2 infection as measured by seroconversion; the secondary outcomes in this analysis for HSV-1 infection; clinical disease. The vaccine and placebo recipients were combined because the vaccine didn't work and the results were identical in the two groups. The acquisition rates were similar in both studies, with some very minor differences. So, the results in both studies were combined in Dr. Langenberg's analysis.

[Slide]

In that data set there were 155 incident

HSV-2 infections, giving good numbers to work with, of which 37 percent were symptomatic and 63 percent were asymptomatic seroconversions. There were 19 incident HSV-1 infections. The infection rate per year was five percent, five infections per 100 person years, that is, five percent of uninfected people acquiring HSV-2 per year, essentially similar in both the partners study and the STD population study.

As predicted and as we pointed out earlier in the broad epidemiologic data, women had a higher risk of acquiring infection than did men. This is an interesting side issue, HSV-1 infection did not change the rate of HIV infection. So, the people who were HSV-1 seropositive at enrollment and those who were HSV-1 seronegative at enrollment had identical rates of acquiring HSV-2. It is fascinating to me, however, that this result is entirely inconsistent with the results from the now GlaxoSmithKline, then SmithKline Beecham, HSV-2 vaccine studies which Dr. Stanbury may talk about later, where, with an essentially identical study design, it in fact was shown that HSV-1 appeared to protect against HSV-2 acquisition--similar design; similar sample size. How that debate as to whether

HSV-1 is protective is going to sort out over time remains a conundrum to me.

[Slide]

Other results from the studies are that 13 percent of the incident symptomatic infections were atypical. Trained observers who are looking to find herpes missed the diagnosis pretty frequently. In fact, if you jump down here, missed diagnosis in either direction--thinking it was herpes when it wasn't or not thinking it was herpes when it was because they presented with these sorts of things--by the investigators and the clinicians who are highly trained and experienced in this disease was in the 20 percent range. With other, more recent data, it is even higher than that. So, it is a disease that can be difficult to recognize.

Many of the asymptomatic seroconverters subsequently developed clinically evident disease. That is truly an underestimate. Some of these people seroconverted, for example, at 12 or 13 months in an 18-month study and only had one more follow-up visits thereafter. So, over a long period of time this undoubtedly would be greater.

Interestingly, half the HSV-1 infections were genital, not oral. The incident infection was

associated with young age and women but not in men. Incident infection was two to three times more common in non-whites than in whites. That also reflects general epidemiologic factors that I haven't otherwise discussed. As we said, HSV-1 did not influence acquisition rate but it did ameliorate incident HSV-2 with more asymptomatic infections. The study design probably reduced the actual real-world infection rate because of the need for ongoing strict safer sex counseling as part of the protocol.

[Slide]

Other factors in herpes transmission, avoidance of sex if symptomatic I have highlighted because I am going to briefly mention them. My time is about up and I will be quite quick at this point. For those of you who are watching the clock, I apologize.

Other things that are associated with transmission are that more recent infections are more transmissible than more prolonged infections. A shorter duration of relationship, apparently independent of duration of infection, is associated with increased transmission rates, presumably having to do with such things as frequency of

intercourse and perhaps--who knows?--less judgment in terms of when to have intercourse in people whose sexual relationships are driven more by passion than by conscious thought. That is my hypothesis for that.

Certainly sexual practices can influence when they interact with virus type; circumcision status perhaps; pregnancy perhaps; immune deficiency and/or HIV status. There have been either conflicting data or speculation around these issues without a lot of data so I won't go into them in any more detail.

[Slide]

There are two condom studies out there. Both are also spin-offs from the Chiron vaccine study. Anna published this one a couple of years ago. It is cited in your handout. Basically, in the monogamous couples of the Chiron vaccine data set with 25 percent common use used as a cut-off because that was the median--it was sort of where the natural break point was in terms of numbers of people available for analysis--clearly reduced transmission from men to women but there was no evidence of protection of women to men. These data were misinterpreted in some sources, as you can

see, even though this odds ratio makes it look like there is actual risk of transmission, the broadness of the 90 percent confidence interval really just tells you the sample size was inadequate to draw conclusions at all.

[Slide]

This slide is data that have now been analyzed by Dr. Langenberg and by Dr. Wald, presented in abstract form and I understand are being prepared for or perhaps are submitted for publication, looking at the high risk group recruited from the STD clinic with 18-month follow-up. In this group the breakpoint in terms of the portion who used condoms was at a different level. It was plus/minus 65 percent. But in this analysis there was demonstrated protection, with a roughly 40 percent reduction in HSV-2 seroconversion rate in common users versus non-users in exposed men.

[Slide]

So, in the next slide I draw the conclusion that although it is very hard to study condom use in a definitive fashion because of the whole nature of how you do those studies, and so on and so on, I think we can draw the firm conclusion

that condoms are partly effective. Previous controversy not withstanding, they are probably equally effective or nearly so for protecting women from male infection and females from male infection. Of course, condoms fall down in their efficacy in use effectiveness and overall acceptability. One might guess better performance in female condom because of greater surface area covered but no data are available.

[Slide]

In the interest of time I will just say there are good data to support the notion that couples who are aware of a herpes discordance in a relationship and who avoid sex when symptoms are present do have lower acquisition in transmission rates in those relationships.

[Slide]

The counseling of persons with herpes--these are again from the CDC 2002 treatment guidelines, with the exception that in terms of what people ought to be counseled I have inserted in highlight the term antiviral therapy, question mark, because that is what your focus is going to be today.

[Slide]

My final slide is simply to make the point that when I wear my public health hat as someone responsible for SV prevention in a metropolitan area of 1.7 million people, and with some interest in and work at national and global levels as well, these are what I think are the six key issues, according to my lights. Some of you might lump these and come up with fewer and some might split them and come up with more but it is not a bad representation of what I think are the core current public health issues in genital herpes. I have highlighted the ones that I think have some relationship to your discussions today.

Preventing sexual transmission and how to best do it is a core issue. The relationship of HSV-2 to HIV and its prevention is a core issue. The under-diagnosis of genital ulcer disease--I would actually say that I think in terms of under-recognition and under-attention to this disease, I think the public health community in general is probably more lax than the practicing community. Few health departments are paying the attention to this disease that it needs or deserves. The role of and when and how to use type-specific serological testing is an issue of

ongoing debate. I will say I believe it is grossly under-used but I think that is a core issue. Under-treatment, leaving aside the transmission issue, is a big issue that, in turn, relates to clinicians' lack of understanding of the psychosocial impact and, of course, preventing the single most frequent devastating outcome, neonatal herpes and attendant maternal morbidity, is the last.

Thank you very much for your attention.

DR. GULICK: Thanks for the overview, Dr. Handsfield. We have time for a couple of questions, if there are questions, for Dr. Handsfield from committee members. Dr. Mathews?

DR. MATHEWS: That was a great overview, Hunter. Is there evidence of uniform type-specific immunity?

DR. HANDSFIELD: Well, yes but, first of all, it does not cross specificity. There is not cross immunity between HSV-1 and HSV-2. The general consensus is that it is extraordinarily rare at the clinical level for people to get ping-ponged, that is, new HSV-2 infections if they are already HSV-2 seropositive.

Now, there are no absolutes in biology of

medicine and it would be very difficult to know if, for example, the occasional patient who, three years into a pattern of recurrences occurring three or four times year, now all of a sudden has six or eight occurrences a year, did that person get a new infection on top of it? There is no evidence that that happens. If it happens it is very rare. We do know from the Chiron and extrapolating from the GlaxoSmithKline vaccine studies that neutralizing antibody alone does not provide protection against exogenous infection. But the notion that there is strong type-specific immunity that involves some combination of cellular and other mechanisms we don't understand I think is epidemiologically solid, but there are others in the audience who could probably answer your question with more scientific precision than I just have.

DR. GULICK: Dr. Kumar?

DR. KUMAR: Would you be able to comment on why it is more common, HSV-2, among African-Americans?

DR. HANDSFIELD: Yes, I intentionally avoided that issue because though I think it is epidemiologically interesting, I think it can be distracting to get too much into racial issues for

a whole variety of reasons that you are very well familiar with. That said, whatever drove the prevalences to very high rates, after you adjust for age, sex and geography, fairly consistently African-Americans have much high HSV-2 seroprevalence rates than do whites, Asians and some other ethnic groups, and Hispanics and native Americans tend to be in the middle. Whatever the reason that got it there, once it gets to that point the average sexually active person is more likely to encounter an infected person. So, sustained rates do not imply ongoing levels of sexual risk-taking that you might assume just that the prevalence is high.

Now, why they got there to begin with clearly has to do with issues that are fairly poorly understand by sexual partner networks, partner selection and that sort of thing. The whole issue of overall higher HSV rates in African-Americans compared to whites probably relates to such things as higher mortality rates and higher incarceration rates in African-Americans that change the male-female ratios in communities and affect sexual partner networks, and a whole host of other very complex issues. So, that is a

fairly inadequate answer but I think that is about as far as the science allows us to go with it.

DR. GULICK: Yes, Dr. Guinan?

DR. GUINAN: I wonder about the source of asymptomatic shedding. Where have these cultures been taken? Theoretically, the virus could shed anywhere along the distribution of the nerve, which is a long way. Traditionally, you know, the vagina in women has been cultured and maybe the labia, but in men it is not clear to me that there are samples taken from suspect areas that might be shedding. Are there well-established negative studies that it doesn't shed in some places and does in others?

DR. HANDSFIELD: In the interest of time I didn't go into the methodology behind those studies. Briefly, what is done is that patients are trained to self-collect specimens, attempting to get a cervical specimen in women which really means putting a swab at the end of the finger and attempting to reach the cervix for at least a high vaginal and introital sweep and perianal sweep, and those are collected every day and go to the laboratory. Couriers come and pick them up, and that sort of thing.

In men, and Anna, correct me if I am

wrong, I think the technique is a swab in the urethra, under the foreskin or around the glands and up and down the shaft, and a third swab also perianally. As a side note, a modest proportion of subclinical shedding in heterosexual men occurs perianally, having to do undoubtedly with that broad neural distribution that you suggest.

So, that is the basic technique. The frequencies of subclinical shedding tend to be slightly lower in men than in women, but that is probably an artifact of the notion that, first, cultures may be less sensitive on dry skin and PCR for that matter and, second, because men probably recognize subtle lesions more readily than some women do and, therefore, more men with recurrences classify themselves as symptomatic than women do.

DR. GUINAN: Scrotum, for example, might be a source and, of course, condoms don't cover scrotum so it would make sense that in asymptomatic--

DR. HANDSFIELD: Anna, have you tested scrotum? Is scrotum one of the sites that you have been surveying?

DR. WALD: Not routinely.

DR. HANDSFIELD: Not routinely?

DR. GULICK: I am sorry, we need you to go to the mike and identify yourself and answer the question. Thanks.

DR. WALD: Anna Wald, from the University of Washington. In men, we have them mostly swab normal-appearing penile skin for asymptomatic shedding and also the perianal area. Urethral swabs in general are negative and we have moved away from those. We have looked at scrotum in a small number of men and it did not yield virus, but it was a small sample.

DR. GULICK: I would like to ask one last question and then we need to move on. I was intrigued by your recommendation that people at high risk for HIV actually have an HSV-2 serology done. Two questions from that. One, what is the mechanism of action that increases the acquisition of HIV? Number two, what would you do with that result practically?

DR. HANDSFIELD: As far as the first question, I am not an immunopathologist so I am probably not the best to answer but I think the general notion is, as you well know, that shedding is associated with lesions; they are simply not visible in an inflammatory reaction at the surface,

and those inflammatory reactions bring CD4-laden inflammatory cells to the surface so that there is a biological enhancement of potential infection above and beyond, and in addition to the potential mechanical mucosal disruption. I think there is a general consensus that something like that is going on. Others may elaborate in more detail than I can.

What would you do? Well, I guess I would answer the same way I would answer what do you do with HIV testing and counseling to begin with. There is a lot of controversy about how good it is in helping people understand their risk and helping them prevent transmission. But what we do know is that it can't hurt. So, from a public health standpoint, I think it is clear that people who are HIV susceptible and HSV-2 infected, that some individuals, not all and maybe not even a high proportion, we don't really know, will, with that knowledge say--I mean, it will help some people click and the person who is sort of on the fence about where and how he or she is going to select partners, whether to use condoms or not, maybe now clicks over and that is the deciding factor that helps them reduce their risk.

So, my argument is that it cannot hurt and very likely, on a broad population level, will help. So, the quick answer is I would counsel them accordingly about their increased risk and use that to help them protect themselves.

The other issue is should HIV-infected people also be tested? That is actually a reasonable issue as well. Whether those people would be more efficient HIV transmitters is less clear from the available data. Then the issue is will it help clinicians be alert for clinical disease that will lower their treatment threshold for certain syndromes. I think that probably depends a little bit on the dedication and clinical acumen of that particular provider as much as anything else.

DR. GULICK: Thanks. We need to move forward. Thanks again for the presentation. Next up is the presentation by the sponsor, GlaxoSmithKline. Dr. Cocchetto will be introducing this.

Sponsor Presentation

Introduction

DR. COCCHETTO: Good morning, Dr. Gulick, Dr. Birnkrant, members of the committee, FDA and

guests.

[Slide]

On behalf of GlaxoSmithKline, thank you for the opportunity to share the results of a major clinical study with valacyclovir, also known as Valtrex. My name is David Cocchetto and I am a member of the team at GlaxoSmithKline that studied the ability of suppressive therapy with Valtrex to reduce the frequency of transmission of genital herpes.

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Over the next 45 minutes my colleagues and I will summarize this work. I will briefly summarize the regulatory history of this study and show the statements that GSK is seeking in product labeling. Following my introductory remarks, Dr. Stuart Harding will present the design, methods and results of the clinical study. Finally, Dr. Clarence Young will provide concluding remarks.

[Slide]

Dr. Handsfield has presented an informative overview of genital herpes, including information on transmission. The current approaches to reduce transmission of herpes are abstinence, avoidance of sexual contact during

symptomatic episodes of genital herpes, and use of condoms during sexual contact even if symptoms are absent.

However, as you have heard, these approaches are incompletely effective. Further, no prophylactic vaccine or topical microbicide is currently licenses or likely to be registered in the next three to four years. Therefore, an unmet need exists for additional approaches to reduce transmission of genital herpes.

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Valtrex is currently approved for use in the United States for several indications, as listed here. One of the approved uses is suppression of recurrent episodes of genital herpes. Suppressive therapy with Valtrex was approved by FDA for immunocompetent individuals in September of 1997, and for patients with HIV infection in April of 2003.

[Slide]

For study HS2AB3009, which I will refer to as the 3009 study, GSK and FDA have had a proactive, constructive dialogue about this study since the topic was first introduced in 1995. We appreciate the time and expertise of FDA in

providing their guidance on the design of this study. Extensive feedback was obtained in a meeting with FDA in September of 1996. That meeting, as well as subsequent dialogue, enabled GSK to design a single adequate and well-controlled trial to evaluate Valtrex. Ultimately, the study was completed in March of 2002, and a supplemental application was submitted on October 31.

In GSK's pre-study discussions with FDA we received three main items of guidance regarding the design and conduct of this study, and I will now summarize these items for you.

[Slide]

FDA's first item of pre-study guidance pertained to the primary endpoint. FDA advised strongly that the primary endpoint be acquisition of clinically symptomatic, laboratory-confirmed genital herpes in the susceptible partner. Importantly, this primary endpoint is able to demonstrate clinical benefit to the susceptible partner. FDA advised that a single large clinical study should yield strong evidence in order to be convincing. That is, 70-80 percent reduction in transmission. At GSK, we adopted this primary endpoint and designed the study to detect a 75

percent reduction in transmission of genital herpes.

[Slide]

FDA's second item of pre-study guidance to GSK was that a robust analysis of clinical safety is required for Valtrex in this relatively health population receiving suppressive therapy. We responded to this advice in the 3009 study itself where we collected clinical safety data for the 743 source partners receiving Valtrex for eight months. In addition, in other clinical studies of suppressive they we collected clinical safety data for over 1,500 additional patients who have received Valtrex for 6-12 months. All of these safety data have been provided to FDA in previous submissions.

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Finally, FDA emphasized the importance of GSK assessing the efficacy of Valtrex in addition to current public health recommends for safer sex counseling and use of condoms. We designed the study to provide all patients with safer sex counseling and encouraged use of condoms during all sexual acts. Therefore, our objective was to demonstrate the incremental benefit of the addition

of Valtrex to safer sex counseling and use of condoms.

In summary, we designed the 3009 study to incorporate each of FDA's main items of pre-study guidance to GSK. Subsequent speakers will present results showing that suppressive therapy with Valtrex is safe and effective for reduction in transmission of genital herpes.

[Slide]

We are seeking an addition to the prescription drug labeling for Valtrex based on the 3009 study. On this slide, in white text, I am showing the current FDA approved indication statement for genital herpes. We propose to add the yellow text based on the 3009 study.

Further, a description of study 3009 is proposed for the clinical trial section of the labeling, and this description has been provided in your briefing document.

[Slide]

Let me move on and introduce Dr. Harding. Dr. Harding will present a summary of the study design, methods and results. Thank you.

Study Design, Methods and Results

DR. HARDING: Thank you, David. Good

morning, everyone.

[Slide]

As Dr. Cocchetto said, I am going to describe to you the conduct and results of study 3009 but, before doing so, I would like to make some introductory remarks.

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First, we were set a considerable challenge in being able to demonstrate what was described as a substantial reduction in transmission between partners, between 70 and 80 percent and with symptomatic clinical disease as the endpoint.

Second, the study was demanding and personally intrusive for the couples participating. Furthermore, it was difficult to find serodiscordant couples who were in a stable relationship. As a result, it took over three years to screen and recruit couples, and involved over a hundred sites internationally.

Finally, I would like to thank Dr. Larry Corey, of the University of Washington, for helping us develop a protocol, reviewing the endpoints and interpreting the results. He served as chairman of the endpoints committee in his laboratory under the

direction of Dr. Rhoda Ashley Morrow who performed the virology assays. He and Rhoda are here today and are available as experts to join the discussions.

What I will demonstrate to you in the course of this brief overview of the study is that we achieved our objective with a 75 percent reduction in the transmission of symptomatic genital herpes.

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The scope of my presentation covers the following topics.

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So let me begin with the rationale for the study. First, there is the proven efficacy of Valtrex in suppressing the recurrences of genital herpes. Second, as you have heard from Dr. Handsfield, shedding of HSV-2 occurs not only around the time of an episode but in between episodes, such that it is being estimated that up to 70 percent of transmissions occur in the absence of lesions. It is the virus that is shed that is the source of transmissible infection. We also know that Valtrex reduces viral shedding. Therefore, taking all these points into

consideration, it is hypothesized that daily suppressive therapy with Valtrex will reduce the frequency of transmission of the herpes virus.

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Moving on to design considerations--

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--these are some of the major factors we considered and I will deal with them one by one. Before I do so, I would like to emphasize that a trial design that would allow one to demonstrate reduced transmission requires stringent criteria to make it both manageable and interpretable. When we applied these criteria we found that there was really only one design that allowed us to test the hypothesis.

First, the study population actually comprised a couple. Let me orient you straightaway to the concept of the source partner and the susceptible partner. The source partner had to have recurrent genital herpes, confirmed by HSV-2 seropositive status and had to be a candidate for suppressive therapy with Valtrex. This is an important consideration since we have a unique situation where one person is treated to potentially benefit another. For this clinical

trial we felt there had to be a potential benefit for the source partner as well. So, it was the source partner who was given study drug. The susceptible partner had to have no history of genital herpes and had to be seronegative for HSV-2. It was the susceptible partner who is monitored for the acquisition of HSV.

In order for us to study this in as controlled a setting as possible, we stipulated a monogamous relationship. We did not want the susceptible partner having sexual contacts with others not on study drug. To limit the number of variables we enrolled heterosexual couples only.

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As I just mentioned, the source partner had to be a candidate for suppressive therapy and was allocated Valtrex or placebo. We selected source partners with nine or fewer recurrences per year, which encompasses about 80 percent of those with symptomatic disease and for whom an approved dose of Valtrex is 500 mg once daily.

As for the duration of dosing in this study, eight months was chosen based on several considerations. I have already mentioned the demanding and personally intrusive nature of the

study procedures. In addition, we were concerned about a possible increase in partner switching over time and a reduction in acquisitions with time, as shown in the prior Chiron vaccine study.

What we did do to encourage enrollment and provide an ongoing commitment during the study was to offer open-label Valtrex at the end of the study for a further 12 months. This also gave us the opportunity to obtain further long-term safety data.

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Moving on to sample size calculations, the transmissibility of HSV-2 is quite variable. Depending upon the population studied, the range is somewhere between 1/40 and 1/1,000 or more sexual contacts. Transmission acquisition has been reported between 3.5 and 10 percent over the period of a year. Considering that our population might be a somewhat low risk one and that the study was of only eight months duration, we estimated that the rate of acquisition in the absence of treatment would be about three percent. In looking for 75 percent reduction in transmission this would translate to 0.75 percent rate of Valtrex.

Now, calculation based on these estimates

yielded the number of susceptible partners acquiring symptomatic clinical disease to be 28 to provide 90 percent power to differentiate between active and placebo. Given our assumptions of acquisition rates, we would need 1,500 couples to be enrolled.

[Slide]

Moving on to stratification and randomized, we already knew that women were more susceptible than men in acquiring the disease and it appeared that antibodies to HSV-1 might afford some degree of protection against acquisition of HSV-2, especially in women. So, we stratified treatment based on gender and HSV-1 serostatus of the susceptible partner. Our original intent was to recruit more female susceptibles in order to capture more cases of transmission, but had to abandon this due to difficulties in recruiting adequate numbers.

[Slide]

Having stratified enrollment by gender and serostatus of the susceptible partner, it was the source partner who was allocated Valtrex or placebo as shown here. I would like to point out that there were equal numbers of Valtrex and placebo for

each block but we didn't require equal numbers block to block. The centralized randomized and stratification system was used.

[Slide]

It was very important that couples understood the principles of how the herpes virus could be spread and how they could help prevent transmission. This is clearly laid out in a very informative American Medical Association's educational booklet, "genital herpes, a patient guide to treatment." A copy of this booklet was given to each couple. For non-English speaking subjects translations of this booklet were provided.

[Slide]

In addition, all were counseled at screening, enrollment and each follow-up visit on how to practice safer sex. The principles of safer sex, we emphasized, were to avoid sex whenever the source partner has signs or symptoms of genital herpes and use condoms for every sexual contact, whether vaginal, oral or anal.

In addition to safer sex counseling, source partners were treated if they had an episode of genital herpes whether they were on active or

placebo. Study medication was stopped and they were given open-label Valtrex, 500 mg twice daily for five days. However, it should be noted that the couples remained in the study,, with the source partner returning to double-blinded study medication at the end of the five days.

So, taking these factors into consideration, we were doing all we could to ensure prevention of transmission. Any benefit of Valtrex suppressive therapy would be above and beyond these measures.

[Slide]

Now moving on to study methods, I have already made mention of some of these in my introduction. For example, I have already indicated that this was stratified and randomized, double-blind, placebo-controlled and that it was carried out in a large number of centers around the world. In fact 96 centers contributed couples who participated. The study population was otherwise healthy and 18 years of age and older.

[Slide]

For both partners there was a monthly clinic visit. For both there was a review of a diary. For the source partner whether they had had

any signs or symptoms of genital herpes or any adverse events. For the susceptible partner both any signs and symptoms of genital herpes and a record of the type and number of sexual contacts and whether condoms were used. Diary interviews were performed separately to allow more frank evaluation. Both partners were counseled on safer sex practices and condoms were offered. The susceptible partner had a blood draw for serology and the source partner returned the study drug for drug accountability.

[Slide]

Regardless of the monthly visits, if a susceptible partner thought they had signs and symptoms of genital herpes they were to go to the clinic as soon as possible for examination, swabs and serology. On days one, five and ten of the suspected episode one swab was taken for culture and one for PCR. All samples of swabs and sera were sent to the University of Washington, with the exception of culture swabs from Canada which were sent to a Canadian lab. If a clinical diagnosis of genital herpes was suspected, they were given treatment appropriate for an initial episode according to approved product label. However, the

couple remained in the study until a definitive diagnosis was made based on the lab tests. If the diagnosis was confirmed they were considered to have completed the study.

[Slide]

The primary endpoint was, as agreed with FDA prospectively, the acquisition of symptomatic genital herpes infection by the susceptible partner. The diagnosis was based on the susceptible partner having signs and symptoms commensurate with genital herpes confirmed by one or more laboratory tests, culture, PCR and/or seroconversion. Any positive culture for a primary endpoint was assessed for sensitivity to acyclovir as transmission of resistant virus would have been of considerable concern. Each case where there were signs and symptoms was to be reviewed by an endpoints committee.

[Slide]

The endpoints committee was convened at the end of the double-blind portion of the study when all the laboratory data were available. The purpose was to determine whether each case met the criteria for being considered a primary endpoint. It is important to note that the committee remained

blinded to treatment during the review process and that the committee worked to written guidelines and minutes were recorded.

[Slide]

The secondary endpoints were as described on the next two slides. For the susceptible partner the time to acquisition of symptomatic infection is another way to look at the primary endpoint but has the benefit of comparing groups throughout the study and takes account of duration of study participation. We were also interested in the proportion of couples with and time to overall acquisition. This now includes those who acquired infection without symptoms, as demonstrated by seroconversion alone, added to those with the primary endpoint.

The secondary endpoints of the source partner, which formed the basis for our hypothesis, were the time to first recurrence of genital herpes and the effect of Valtrex on viral shedding, which was carried out in a substudy and which I will describe in just a moment.

[Slide]

Other secondary endpoints are shown here. First is the proportion of couples with HSV-2

seroconversion. Note that this could have included those with symptoms or not, and a subset of this which is those with asymptomatic seroconversion alone. We also planned to assess any HSV-1 genital acquisitions but there were none. We also looked at the time to first oral outbreak of herpes in the source partner. I am not planning to show the results of any of these other endpoints in my presentation but would direct you to the briefing document which has this information.

[Slide]

As I said, the effect of Valtrex on HSV-2 viral shedding was assessed in a substudy. This involved 89 source partners from three U.S. sites. The subjects were still blinded to treatment so may have been on Valtrex or placebo. Swabs were collected every day for 60 days for quantitative PCR assay.

[Slide]

Now for the results which you have all been patiently waiting for. These are presented under three broad headings, a description of the study couples; the results for the primary endpoint with subanalyses; and the results for secondary endpoints. I will start with the study couples.

[Slide]

If you recall, the aim of our program was to enroll 1,500 couples. We enrolled 1498. Of interest is that over 4,000 couples came forward to take part in the study but more than 2500 were found ineligible. The most common reason was that the susceptible partner was already HSV-2 seropositive. Of the couples randomized, 1,484 comprised the intent-to-treat population, with 743 source subjects randomized to Valtrex and 741 to placebo.

[Slide]

Now for subject accountability, 78 percent of the subjects completed the full eight months in the study and reasons for discontinuation are given in the table. There were more consents withdrawn on placebo than on Valtrex, which anecdotally appeared to be due to recurrences in the source partner, but there were equal numbers lost to follow-up or dissolution of the relationship. The other reasons category included relocation, pregnancy, adverse events and protocol violation.

However, some data were available from 96 percent of the intent-to-treat population because all but 58 couples returned for one or more visits

and sometimes as many as six or seven. Having these data was particularly a value in the time to event analyses.

[Slide]

Recruitment by region is shown on this slide and shows that over half the couples were from the U.S.A., with over 60 percent recruited from North America including Canada.

[Slide]

Moving now to demographics, this set by the stratification variable, gender and HSV-1 serostatus. The majority of susceptible partners were male, which is in keeping with the higher prevalence of the infection in women who formed the source. HSV-1 serostatus, of note almost 70 percent susceptible partners were already HSV-1 seropositive.

[Slide]

Ages and race were well matched between groups, with a median age of 34 years and 90 percent of subjects white.

[Slide]

The Valtrex and placebo groups were also well matched for the items on this slide, the number of recurrences of genital herpes in the

source partner, the duration of infection in the source partner, the duration of the monogamous relationship and the frequency of vaginal sexual intercourse. However, about 50 percent, as you can see at the bottom of the slide, claimed never to have used condoms in the month prior to randomization.

[Slide]

I will now deal with the primary endpoint. What I will do, I will take you through the endpoint evaluations, the proportion of clinical acquisitions, the time to clinical acquisition and some subanalyses of this primary endpoint.

[Slide]

First let me show you how the numbers play out. Of the original 1,484 couples in the ITT population, 58 never returned, leaving 1,426 for whom we have data; 71 susceptible partners had some sign or symptom thought suitable to be put forward for consideration by the endpoints committee. The remaining 1,355 remained asymptomatic.

[Slide]

Of the 71 referred to the endpoints committee, 20 were confirmed as true clinical acquisitions or primary endpoints, 15 by

seroconversion with or without culture and/or PCR and five by culture or PCR alone. Fifty-one were rejected. Of these, the majority had no confirmatory laboratory result. However, there were three symptomatic subjects who seroconverted but were rejected by the committee. The reasons for rejection for two of them were that the symptoms were considered unrelated to genital herpes. The third was considered a protocol violator in that the source subject had only eight doses of study drug. There were also 18 HSV-2 seroconversions from the asymptomatic group, making a total of 36 seroconversions and 41 overall acquisitions.

[Slide]

Looking now at the primary statistical analysis which was a proportions analysis, of the 20 confirmed primary endpoints, 16 were on placebo and four on Valtrex. These represent 2.2 percent and 0.5 percent of their respective populations, as shown on this slide. This difference is statistically significant with a relative risk of 0.25. In other words, there was a 75 percent reduction in the risk of transmission of genital herpes when the source partner was on Valtrex

compared to placebo. This then met our a priori expectation and confirmed our result as being both substantial and clinically meaningful.

[Slide]

Looking at the time to acquisition for these primary endpoints using a Kaplan-Meier plot, as shown here, again there is a clear and statistically significant difference between Valtrex and placebo in favor of Valtrex. Of note is that the difference becomes apparent almost immediately after randomization and that the rates of acquisition remain linear throughout the study, with no indication of tailing off with time. I will mention here that we have viral cultures from ten of the subjects with primary endpoints and all isolates were sensitive to acyclovir. In other words, their IC-50 values were below 2 mcg/ml.

[Slide]

I am now going to show you some subanalyses of the primary endpoint, this one by gender. As expected, the majority of acquisitions were in females. There were 12 in total of the 20, this despite the smaller number of female susceptible partners enrolled in the study. The difference between males and females was

statistically significant but the difference is in favor of Valtrex regardless of gender.

[Slide]

We had also expected more acquisitions in HSV-1 seronegative partners but there wasn't a major difference, as shown here. The trend was for proportionally more acquisitions in seronegative subjects but the numbers were small and not significant. However, again differences were observed in favor of Valtrex regardless of HSV-1 serostatus.

[Slide]

Finally, here is a display of acquisition by condom use. The chart here shows the frequency of acquisitions of symptomatic genital herpes for the placebo group according to whether the median use of condoms during the study was "never," "sometimes" or "nearly always." The incidence reduces from 2.8 percent for those who never used condoms to half that, 1.4 percent, for those who nearly always used them.

[Slide]

Now I have added the data for Valtrex and the message is the same. Note that there were zero acquisitions in the sometimes and nearly always

categories. This emphasizes the importance of couples practicing appropriate protective measures and shows that the benefit of Valtrex is in addition to the practice of safer sex. In a covariate analysis the effect of condoms in reducing transmissions approached statistical significance, with a p value of 0.06.

[Slide]

Now for the secondary endpoints and I will deal with the following, first I will look at recurrences in the source partner; then viral shedding from the source partner in the substudy. If you recall, the hypothesis was that if we could reduce recurrence and viral shedding we should also be able to reduce transmissions. Finally, I will show you the effect of Valtrex on overall acquisitions. Again to remind you, these were all HSV-2.

[Slide]

Here we have a graph of the proportions of source partners for genital herpes recurrence at eight months, 47 percent for Valtrex and only 13 percent for the placebo-treated subjects. This is a highly significant difference and similar to that reported in previous studies.

[Slide]

Now we have the results from the viral shedding substudy which showed a reduction in shedding by Valtrex. I will give you the results for total shedding, which are those obtained from every day of swabbing which is of 60 days duration. These included days on which there might have been an outbreak. I will mention results from an analysis when those days are excluded. Eighty-nine subjects were enrolled in this substudy and the numbers are somewhat unbalanced, 50 on placebo and 39 on Valtrex. This was because randomized to the main study, if you recall, was centralized, not by site. It was also dependent upon the source partner's agreement to undergo the extra study procedures necessary.

The results were very much as expected from the literature, as we have just heard, with HSV DNA being detected by PCR on at least one day in over 80 percent of those on placebo compared with almost 50 percent on Valtrex. HSV DNA was detected in almost 11 percent of days for those on placebo compared with almost three percent on Valtrex. That is a 73 percent reduction on Valtrex. The number of DNA copies was reduced on

Valtrex from 4.2 on a log scale to just 1.7. That is greater than 99 percent reduction. All these differences were clearly statistically significant.

Very similar results were obtained if one excludes days when there was an outbreak. There was still 90-95 percent reduction in DNA copies/mL on Valtrex compared to placebo.

[Slide]

Just to remind you before I get to overall acquisitions how that group is defined. It is those with a primary endpoint, some confirmed by seroconversion with or without culture and some by culture or PCR alone, and to those you add those with seroconversion and the total is 41.

[Slide]

So here we have the proportion of susceptible partners with overall acquisition of HSV-2 infection. Twenty-seven of them were in the placebo group and 14 in the Valtrex group. This represented a relative risk of 0.52 or a reduction in risk of 48 percent.

[Slide]

The time to event analysis for this group, shown here, is more powerful statistically as it adds time of acquisition to the numbers of

acquisitions. The reduction in risk on Valtrex was, as in the previous slide, 48 percent for the relative risk of 0.52. As with the primary endpoint, the difference in rate was noted early and remained linear throughout the study. So, the secondary analyses fully support our hypothesis and add strength to the primary analyses.

[Slide]

I will now briefly review the safety results obtained in the study. Remember that these pertain to the source partner who is receiving Valtrex or placebo. These results are from the 8-month double-blind portion of the trial. I will mention results from the 12-month open-label extension at the end.

[Slide]

This slide summarizes the adverse events reported through the study. As you can see, there is very little difference between Valtrex and placebo. None of the serious adverse events was classified as drug related. Discontinuations due to an adverse event were slightly more frequent on Valtrex but none of these was serious or unusual. Reasons included headache, gastrointestinal upset and one case of urticarial rash.

[Slide]

Here you see a graphical depiction of those adverse events reported by five percent or more of subjects. The most common events were headache, upper respiratory and gastrointestinal, and there was nothing unexpected from previous experience in clinical trials.

[Slide]

Laboratory tests included those listed above as being of greater potential interest, reflecting hepatic, renal and hematologic systems, were unremarkable and there was no indication of any difference between Valtrex and placebo.

[Slide]

Finally, here is a summary of the data we have up to January 31st of this year from 831 source partners who continued for further 12 months on open-label Valtrex after the main study had completed. This represents about 95 percent of those opting to continue to receive drug. The dose of Valtrex was 500 mg once daily as in the main part of the study.

As you see, the pattern of events is similar to that reported in the double-blind phase and, again, we have no new safety signals for what

for some of them is now 20 months of continuous use of Valtrex.

[Slide]

Finally, in conclusion study 3009 clearly met its objectives. By that, I mean that we set out with a hypothesis that Valtrex would reduce episodes of recurrent genital herpes in the source partner and would reduce viral shedding. These would result in a significant reduction in transmission of genital herpes to an uninfected partner. The study demonstrated this with a reduction of 75 percent in the acquisition of clinical infection by a susceptible partner and a 48 percent reduction in overall disease acquisition. This benefit is seen over and above that afforded by counseling on safer sex practices, the use of condoms and, I should add, the treatment of outbreaks in the source partner. The safety profile of Valtrex was similar to that described in the product label which by now has been well characterized.

Thus, I hope to have demonstrated to you that the data are scientifically sound and clinically relevant, and that the reduction in transmission of herpes virus to a partner is an

additional benefit of suppressive therapy when combined with safer sex practices.

Thank you, and I will now pass it over to Clarence Young to make some concluding remarks.

Concluding Remarks

DR. YOUNG: Thank you, Stuart. Good morning, everyone.

[Slide]

My name is Clarence Young and I direct clinical development activities at GlaxoSmithKline for anti-infectives. I have also had the experience in my career of caring for patients with genital herpes and also counseling these patients.

Dr. Harding has taken you through the results for study 3009. My task over the next few minutes is just to summarize what these data mean for both patients as well as healthcare providers.

[Slide]

First of all, it is important to note that study 3009 is a landmark study which provides a new option for the management of patients with genital herpes. As Dr. Handsfield outlined in his talk, various strategies have been undertaken to prevent the transmission of genital herpes but to date none of these strategies has been completely effective,

and the availability of a prophylactic vaccine is still several years away.

This study, 3009, was the first demonstration that an antiviral agent can actually decrease the transmission of genital herpes between sexual partners. This study also indicated an association between the reduction in viral shedding and the transmission of genital herpes. These data may be especially relevant for HSV-2 uninfected women of childbearing potential who are at great risk for acquisition of genital herpes in the course of pregnancy.

[Slide]

The benefits of Valtrex therapy that were observed in this study were in addition to safer sex practices and condom use and the results, as Dr. Harding had mentioned, are truly unique in that the benefits of Valtrex therapy accrued not only to the HSV-2 infected source partner with genital herpes who received Valtrex therapy but also the HSV-2 uninfected susceptible partner who did not receive Valtrex. These benefits were without any added risk to the partner who received Valtrex.

The study, therefore, provides a new option to address what has been shown, and as you

saw earlier in Dr. Handsfield's presentation, to be a major patient concern, which is transmission of genital herpes.

[Slide]

Now, GlaxoSmithKline has had a long-standing interest in the education of patients and families, as well as healthcare providers, regarding genital herpes, its management and various treatment options. It is important to ensure that the patients as well as healthcare providers have a very clear understanding regarding study 3009, how the study was designed; what the results of the study showed; and what the implications of these results are to avoid any misinterpretation of the study results. GlaxoSmithKline will work with FDA as well as with external stakeholders in order to ensure that the benefits of Valtrex therapy and, more importantly, the benefits of safer sex practices and condom use are communicated both accurately and effectively.

[Slide]

Since Valtrex is already available for suppression of genital herpes recurrences, it is reasonable to ask why additional information is required in the prescribing information. Well,

feedback from healthcare providers has indicated that the availability of this new indication for Valtrex will provide another reason for healthcare providers to initiate a conversation with their patients regarding sexually transmitted diseases and safer sex practices. Others view this as another tool in the toolbox which they will use as part of their management approaches to their patients with genital herpes. Awareness of these data by patients may influence their decision to actually pursue suppressive therapy. Finally, the availability of labeling will enable GSK, external stakeholders and patients to have a definitive source of accurate and balanced information on the results of study 3009 with the benefits of FDA oversight.

[Slide]

We cannot say that based on the results of this study the use of Valtrex will impact in any way the prevalence of HSV-2 infection in the United States, or that the study addresses all of the questions which one might have regarding the benefits of Valtrex therapy in special populations. What we can say is that the results from study 3009 clearly provide an opportunity to make a difference

in the lives of patients.

[Slide]

Finally, GSK would just like to acknowledge the participation by the hundreds of individuals in this very time consuming and demanding study. We also would like to acknowledge both the study personnel as well as clinical investigators. Some of them are here with us today. Thank you very much for your attention and for the opportunity to share the results of study 3009 with you today. Thank you.

DR. GULICK: Thanks to Drs. Cocchetto, Harding and Young for the sponsor presentation. As mentioned earlier, we are going to defer the question and answer period until after the presentation from the agency, which brings us to our break. It is 9:55 so we will reconvene at 10:10.

[Brief recess]

DR. GULICK: We will move now to the agency presentation. We will start out with Dr. Haverkos.

FDA Presentation

Study Design

DR. HAVERKOS: Good morning.

[Slide]

I am Dr. Harry Haverkos. I am the primary reviewer on the application, and I will be joined by my statistical colleague, Dr. Smith, in presenting the FDA review.

First of all, I would like to congratulate the sponsor on conducting this large, multinational trial, really a landmark study looking at a medication to reduce sexual transmission of herpes simplex.

[Slide]

Our presentation will be divided into several areas. I will present some comments on study design and Dr. Smith will get to present the efficacy results. I will then come back up and discuss a little bit of the virology, safety and some of the behavioral results. We will then list our conclusions and finally read for you the questions that we would like the committee to deliberate on for us.

[Slide]

As reported before, this application was submitted in October and has an NDA due date of September. They propose the dosage of 500 mg a day of valacyclovir to reduce the risk of transmission

of genital herpes with the use of suppressive therapy and safer sex practice.

[Slide]

Valacyclovir is approved for several indications involving herpes simplex, treatment of initial genital herpes with one gram b.i.d. for ten days; treatment of recurrent genital herpes too mg b.i.d. for three days; and as chronic suppressive therapy of recurrent genital herpes at one gram a day or 500 mg a day as an alternate dose.

[Slide]

This single study was submitted. It is multinational, randomized, double-blind evaluating valacyclovir in HSV-2 discordant monogamous couples. As mentioned, the sample size sought was 1,500 couples. Over 4,000 were screened and the patients were randomized to valacyclovir versus placebo for eight months of therapy. During the study all subjects were encouraged to use condoms and abstain from sex during any outbreaks.

[Slide]

Inclusion criteria were gone through before. These were monogamous heterosexually active couples. The source partner had to be HSV-2 antibody positive and have clinical episodes. They

excluded patients who had greater than ten symptomatic recurrences a year. I am concerned about some of the ethics about not providing suppressive therapy to that group, but it was needed that a person be a candidate for suppressive therapy. It was not clearly defined in the protocol but generally is considered as somewhere between five and six recurrences in a year. The susceptible partner had to be in a relationship with no other partners, and be HSV-2 antibody negative and report no clinical herpes outbreaks.

[Slide]

The primary endpoint has discussed and we will be discussing this point I think over and over again. It is the proportion of susceptible partners with a clinical episode confirmed by the laboratory. The laboratory, of course, could be by culture, PCR and/or serology.

[Slide]

The monitoring that occurred during the study is listed on this slide. Safer sex counseling was provided at each visit. The source partner came in monthly, and during those monthly visits they reviewed the diary card for any symptoms or recurrences that the source partner

had. If they developed an outbreak they were to return to the clinic immediately to be evaluated and to be started on therapy.

Susceptible partners also came back monthly and for those partners two areas were reviewed, the diary cards of the sexual exposures and practices and also looking for any signs of herpes in the previous month. They too were expected to return for any suspect lesion for open-label therapy.

[Slide]

For virology, as mentioned, confirmation was defined by either culture, DNA of suspicious lesions and monthly serologies were followed. Mostly all of the samples were sent to a single lab in Seattle. However, there were five cultures that were sent to a lab in Vancouver.

[Slide]

There were a couple of issues raised I guess by the virologist during our review. In a study with a fairly small number of endpoints I think you really want to make sure that you miss one, two or three endpoints. The samples, as mentioned, were collected at over 100 sites in more than 20 countries from around the world and then

were transported to Seattle. As mentioned, a few Canadian samples were sent to Vancouver.

Concerns are about some protocol violations. There was failure to report at the first sing of genital herpes so some cultures were missed. There were a few samples that were contaminated, a few samples that were lost in transit. Even though herpes is quite a stable virus, there was some concern raised by our virologist about what effect transit might have on some of these results.

[Slide]

As mentioned, there was a long history of discussion between the FDA and the sponsor. As mentioned, there were three topics of discussion. I think our three may be a little different than their three but that probably just reflects more history. The primary endpoint was one of the primary areas of discussion, and we will talk about that again on the next slide.

Source partner inclusion--again, the study was initially looked at as predominantly a serologic study, serologic endpoint. But the FDA wanted really clinical endpoints and so wanted to have the history of clinical herpes of source

partners be candidates for suppressive therapy and less than ten recurrences in the past year was the agreed upon inclusion criteria.

There was some discussion of whether two studies would be better than one. If one studied different populations would it be easier to interpret the results and write the label? In the end, the company I think decided to do one large, multinational study.

[Slide]

The primary endpoint agreed upon is that shown first. We will also be presenting some data on some secondary endpoints, predominantly the endpoint of HSV-2 seroconversion which historically was how the study was initially proposed. Finally, acquisition of meeting one or both of the two endpoints.

I just want to point out question six is actually going to deal with that issue so I think it is very important that we understand the different endpoints.

[Slide]

My last slide before turning it over to Dr. Smith is just to give you a little history of the study. It was initiated in February of 1998.

As mentioned, over 4,000 couples were screened. There were a couple of amendments along the way that occurred. Two of them I think may be part of the discussion. A shedding substudy was added about six months into the study. We will look at some of those results. Then, in May of 2000, because recruitment hadn't quite lived up to expectations, sites were added outside of North American and Europe to include Australia. Eastern Europe was added to those originally recruited from western Europe, and south America. The initial stratification to try to get more female susceptible partners was waived in order to recruit more couples.

With that, let me turn the podium over to Dr. Smith who will present the efficacy results.

Efficacy Results

DR. SMITH: Thank you.

[Slide]

I am going to go over the demographic and baseline characteristics and then primary and secondary results, and robustness of the analyses to discontinuations, and finally regional differences.

[Slide]

One thousand four hundred and ninety-eight out of 4,030 screened couples were randomized. The primary reason for screening failure was the lack of HSV-2 discordance within couples. So, the susceptible partner was HSV-2 seropositive or had symptoms of it.

[Slide]

Demographic characteristics were very similar in both treatment groups so I will summarize them overall. Two-thirds were male and one-third of the susceptible partners were female. The median age was 35 years; 90 percent of the susceptible partners were white; five percent Hispanic; three percent black; one percent Asian and less than one percent other races.

[Slide]

One percent has sexual relations with other partners in the last three months. The median duration with the source partner was two years and 22 percent had been treated for an STD.

[Slide]

Ninety-seven percent had sexual intercourse with the source partner in the last month and the median number of contacts in the last month was seven.

[Slide]

This summarizes the condom use for vaginal/anal intercourse at baseline. Approximately 50 percent of the patients had never used condoms at baseline in both treatment groups. Thirty percent said they nearly always used condoms and about 20 percent said they sometimes used condoms.

[Slide]

In terms of HSV-1 status for female susceptible partners at randomization, approximately 80 percent were positive in both treatment groups. About 20 percent were negative and only two were atypical.

[Slide]

For male susceptible partners, slightly less, about 65 percent were positive. About 35 percent were negative and five were atypical. Again, these were very similar in both treatment groups.

[Slide]

Now I will summarize efficacy evaluations.

[Slide]

The primary analysis looked at clinical evidence of HSV-2 or symptomatic HSV-2 acquisition

and 0.5 percent of valacyclovir patients had clinical evidence of transmission compared to 2.2 percent of the placebo patients. The p value was 0.011 and the odds ratio was 0.24, representing approximately a 75 percent reduction. The 95 percent confidence interval of the odds ratio went from 0.06 to 0.76.

The other two selected secondary endpoints are HSV-2 seroconversion and overall HSV-2 acquisition, which consists of HSV-2 seroconversion or symptomatic HSV-2 acquisition. Some may argue that HSV-2 seroconversion may be a better endpoint because subclinical infections may become symptomatic HSV-2 later on.

Here we have 1.6 percent of the valacyclovir patients with HSV-2 seroconversion 3.2 percent of placebo patients. In this case the odds ratio was 0.49, approximately 50 percent, representing about a 50 percent reduction with valacyclovir treatment. The p value was 0.06. Similar results were obtained for overall HSV-2 acquisition. This was primarily driven by the HSV-2 seroconversion results. In this case we have 1.9 percent of valacyclovir patients compared to 3.6 percent of the placebo patients. In this case

the odds ratio was 0.5.

[Slide]

This is what it looks like graphically. We have a bigger difference for the primary endpoint when you compare placebo patients to valacyclovir patients. Again, the odds ratio is approximately 0.25. Here we have about a 50 percent reduction for these other two selected secondary endpoints, and the p values are of borderline significance. In these analyses withdrawals were regarded as being transmission-free.

[Slide]

When we look at condom use during the study what we have are over 50 percent of the patients never used condoms during the study compared to 30 percent who nearly always used condoms in both treatment groups, and about 15 percent who said they sometimes used condoms. This is calculated a little differently. In this case during the study what they have calculated is the median usage over months one through eight so that basically with nearly always using condoms 90 or more percent of the patients who nearly always used condoms were classified in this category. So, this

represents greater than 90 percent usage at baseline or at a particular visit.

However, because we are using the median to calculate this during the study, it is possible that at one visit they could have nearly always used condoms; at the next visit they might never have used condoms; and at the third visit they might have always used condoms at months one, two and three and, in that case, the median would have been nearly always used condoms. If they never used condoms, that is really zero percent of the time. So, in that case the true median would be about 60 percent rather than 90 percent. So, what we got here during the study is a little different than what we had at baseline.

In addition, condom use can fluctuate from month to month and patients who nearly always used condoms over months one to eight might never have used condoms just prior to an episode. So, we have to take all of this in mind and the study wasn't designed specifically to look at condom use.

[Slide]

Here we have the primary endpoint separated out by condom usage. On the left-hand side we have valacyclovir patients. In this case

one percent of the valacyclovir patients who never used condoms had clinical evidence of transmission compared to 0/91 patients who sometimes used condoms and 0/211 who nearly always used condoms. We have the 95 percent confidence intervals plotted just to indicate that even though we didn't observe any events we have a confidence interval here that ranges from zero percent to over three percent, and here we have more patients so we have a smaller confidence interval that goes from zero to 1.5 percent.

Then, when we look at placebo patients we can see that almost three percent of the patients had clinical evidence if they said they never used condoms through the majority of the visits during the study compared to two percent who sometimes used condoms and approximately 1.5 percent who never used condoms. So, we also see a main effect of condom usage and the more condom usage, the less transmission. The p value for the main effect of treatment, adjusted for condom usage, was 0.011 and the p value for condom usage was 0.08, close to significant. Again, keep in mind that this study was not designed specifically to look at condom use.

[Slide]

To illustrate the effects in a little more detail we also were looking at overall acquisition rates in addition to clinical evidence. So, what we have in the dark shaded regions on the graphs down below is what we saw in the previous slide. Over and above that we have the rates of overall acquisition which can include either clinical evidence or HSV-2 seropositive incidence rates.

So, in this case when we look at the lightly shaded regions for valacyclovir we can see that about two percent who never used condoms had overall acquisition and over three percent who said they sometimes used condoms, and we have the rates for nearly always using condoms of approximately two percent--no real trend for overall acquisition with valacyclovir.

When we look at placebo patients we do seem to see another decline when we look at overall acquisition rates, as is the case when we look at the clinical evidence of transmission. In this case the clinical endpoint is close to statistically significant. It is hard to read here but it is 0.08 and for overall acquisition the p value is 0.84. These p values represent the effect

of condom use.

[Slide]

Now I will talk about the robustness of efficacy analyses to discontinuations.

[Slide]

On the first slide we have the results for the primary analysis. Shown here are the percentage of patients with clinical evidence of having HSV-2 transmission. In this case we have withdrawals and the main point of this slide is to show that the withdrawal rate, which is greater than 20 percent in both treatment groups, is much larger than the percentage of patients with the primary endpoint.

[Slide]

So, we wanted to look at reasons for withdrawal. In this case, the principal reasons include withdrawal of consent, loss to follow-up, relationship breakup and the partner withdrew. Withdrawal of consent was somewhat higher in placebo patients than in valacyclovir patients. It ranged from three to six percent. Six percent of both treatment groups reported loss to follow-up; five percent reported a relationship breakup, approximately five percent; and two percent in both

treatment groups had partners who withdrew.

[Slide]

None of the susceptible partners withdrew to adverse events or lack of efficacy. Less than one percent of the source partners withdrew due to adverse events, although it was slightly higher for valacyclovir, approximately two percent. Less than one percent of the source partners withdrew due to lack of efficacy.

[Slide]

So there were various sensitivity analyses that we used to look at this. One very conservative analysis took all of the withdrawals and considered them to be treatment failures. In this case, the percentage of withdrawals far outnumbered the primary endpoint cases. So, what we have is very little difference between the two treatment arms. In both cases we have approximately 22 percent of valacyclovir patients compared to about 24 percent of placebo patients, and a p value of 0.30. There is no difference when you include all the withdrawals or discontinuations and treat them as treatment failures.

So, what we are getting here are more reasonable estimates when we just include a small

fraction of the withdrawals and treat them as if they were treatment failures. When we assume that 10 percent of the discontinuations were treatment failures we see approximately four percent of placebo patients and we can see approximately three percent of valacyclovir patients. In this case the p value is 0.11. When we count five percent of the discontinuations as treatment failures we see about double the rate for placebo compared to valacyclovir. This looks very similar to the HSV-2 seropositive results, and the p value here again is 0.05 so this is what it takes to reach statistical significance. In the primary analysis none of the discontinuations were counted as treatment failures. They were all concluded to be successes so this is what we see here, with the p value again being 0.011.

The Kaplan-Meier analysis was 0.008. The Kaplan-Meier adjusts for the length of follow-up and also it assumes not informed of censoring. For example, in Valtrex patients the risk for patients who discontinue is the same as the risk of transmission for patients who complete the study. The same thing in placebo patients, the risk for patients who discontinue is the same as the placebo

patients who complete the study.

[Slide]

Now I would like to talk about regional differences.

[Slide]

We see a histogram of the different countries, major geographic regions. In this case, the percentage of patients with a first episode of genital HSV-2 in susceptible partners is plotted and we see that by far the biggest differences seem to occur in Australia and Canada. These are all placebo patients so we have almost nine or ten percent of Australian patients and in Canada it is about three percent, and we have no Valtrex cases except in the U.S. South America has only 43 patients but eastern Europe and western Europe comprise about 20 percent of the sample and there are no cases, no patients who had the primary endpoint in all of eastern and western Europe. The p value for the effect of geographic region was 0.01. So, the main effect of geographic region was very significant statistically.

[Slide]

This is a backup slide which actually has the numbers of confirmed cases in each country.

[Slide]

When we plot the overall acquisition rates we see a similar pattern, with the highest rates in Australia, followed by Canada. However, in Europe we do see cases. In fact, we see more placebo cases in eastern Europe than valacyclovir cases. In western Europe, it looks like they are approximately the same. In the U.S., it looks like the rates ar approximately the same. The U.S. has 803 patients.

This is a little different because for the clinical evidence in the primary analysis the U.S. results tended to look approximately the same as the overall analysis with all countries combined. The other thing is that in Europe it looks like there are as many cases, roughly as many cases as there are in the United States. which is very, very different from what we saw with the primary endpoint.

[Slide]

This is backup slide, which is in your handout, which has the actual numbers of patients.

[Slide]

I looked at several different demographic and other sexual behaviors to see if that could

explain the regional differences. The only thing I was able to see was that it looks like in eastern Europe there is a much higher percentage of patients who said they nearly always used condoms, over 60 percent, compared to all the other geographic regions where it is just slightly over 20 percent or less than 20 percent. However, it doesn't seem like in eastern Europe the rates of HSV-2 seroconversions are any lower. Also, the overall acquisition rate in eastern Europe was similar to the U.S. and western Europe and eastern Europe.

[Slide]

So, my summary and conclusions are that the percentage of dropouts was over 20 percent, and this was much higher than the percentage of susceptible partners classified as having clinical evidence of a first episode of genital HSV-2.

The primary reasons for discontinuation include withdrawal of consent, loss to follow-up and the ending of relationships.

[Slide]

The statistical significance of the primary endpoint depends on the assumptions about how many discontinuations should be counted as

treatment failures. This can be statistical significance or it could also mean clinical significance, i.e., is there a 75 percent reduction, which is actually harder to achieve than statistical significance.

No transmissions were reported in Europe where approximately 20 percent of the patients were enrolled. This rate is similar to the 20 percent discontinuation rate so it is possible that if there were no real treatment differences in Europe then we could also do a sensitivity analysis where we counted those European patients as treatment failures and we would have an equal amount in both groups, and then we would add that on to the percentage of discontinuations and we would have less robust analyses.

[Slide]

The largest treatment effects were observed in Australia and Canada. The U.S. results were similar to the results for the primary endpoint for all countries combined. The differences between valacyclovir and placebo were not as significant for HSV-2 seroconversions and overall acquisitions, particularly in the United States.

[Slide]

Now I would like to have Dr. Haverkos talk about viral shedding, substudy results, safety and behavioral results and conclusions.

Viral Shedding Substudy, Safety and Behavioral Results and Conclusions

DR. HAVERKOS: Thank you, Dr. Smith.

[Slide]

First of all, the viral shedding substudy, 89 patients were recruited and 85 source patients were followed intensively for two months. As mentioned before, they filled out daily diary cards recording any signs or symptoms of recurrence. They collected samples at home and did a self-exam, and then every two weeks came into the clinic for review of the diaries, clinical exams and additional viral cultures.

[Slide]

I think that the results shown are supportive of an effect in suppressing virus. As seen here the valacyclovir group shed 2.9 percent of the days or cultures taken compared to about 11 percent in the placebo group, and during the times of shedding the valacyclovir group had lower levels of virus present, about a one log drop.

I think Dr. Guinan asked some questions earlier about differences, male and female. I have not seen those results and maybe the company can address her question in the comment period.

[Slide]

Moving on to safety, currently the drug has warnings in the label about thrombotic thrombocytopenic purpura and hematuria syndrome and death that has occurred in some patients with advanced HIV disease and immunosuppressed for other reasons, transplant recipients receiving valacyclovir up to eight grams a day. So, there are some significant side effects seen with this but generally at much higher doses than people are going to propose to use for this indication. Adverse events commonly reported with use of valacyclovir include nausea, headache, vomiting, dizziness and abdominal pain.

[Slide]

Looking through the data presented, there were no deaths. There were no reports of TTP/HUS in the study. Twenty-six subjects developed serious adverse events. There were 17 discontinuations and there were 16 pregnancies, and we are looking at those last three bullets on the

next three slides.

[Slide]

If you look at the serious adverse events, they are pretty similar between the two groups. A patient discontinued to glomerulonephritis was a patient that, right at the beginning of the study, developed some symptoms of arthralgias that ended up in a diagnosis of lupus and during that process the patient was discontinued from valacyclovir.

We have one cancer in each column. We have an intestinal obstruction attributed to another medication that the patient was taking. Then we can see some parallels, some spontaneous abortions; uterine fibroids; Bartholin's cyst infection; ovarian cyst; a couple of localized infections. I think one with meningitis came in, was treated with cephtriaxone and was signed out as a viral meningitis though it was not clear that herpes cultures were done or herpes was ruled out in that case but the patient's symptoms resolved over four days and the patient was discharged. There were a couple of orthopedic problems in each group and then a syncope, a vasovagal attack. So, nothing jumping out that one could attribute to valacyclovir and serious adverse events.

[Slide]

If you look at the discontinuations, there were 12 in the valacyclovir group, most of them for symptoms that were attributed to headache and GI disorders. There were two rashes and two where they had renal problems, one glomerulonephritis associated with lupus and hematuria that did not meet any other conditions for TTP and was being worked up for kidney stone.

[Slide]

As I mentioned, there were eight pregnancies in both groups. Trying to look at what impact, if any, valacyclovir might have on these pregnancies, there were four women, source patients randomized to valacyclovir, two healthy infants were delivered and two developed spontaneous abortions. There were seven in the placebo group, as you see here, and three health infants and three spontaneous and one elective abortion. There was one susceptible partner who was treated with valacyclovir for a suspicious HSV initial event who elected abortion, and then there were four other susceptible partners who did not receive drug and for which data was not presented.

[Slide]

Moving on now to the behavioral aspects, just for review, the guidelines put out by the public health service, specifically the CDC, to manage herpes are quite extensive. They are included in your packet. It is mentioned that for critical management of herpes counseling be done. The goals of counseling are to help patients cope with infection and to prevent sexual and perinatal transmission. They are encouraged to inform their partner before initiating a sexual relationship and are reminded that transmission can occur during asymptomatic periods as well as during outbreaks.

[Slide]

In addition, partners or couples are encouraged to abstain from sex when lesions or prodromal symptoms are present. They are encouraged to use condoms which, when used consistently and correctly, can reduce the risk, again reemphasizing that sex partners might be infected even if no symptoms occur, and encouraging testing of partners for herpes.

[Slide]

These guidelines are pretty much based on a variety of studies from the Seattle group, including a study in JAMA in 2001 which the authors

claim was the first one to prove that condoms actually prevented transmission or reduced transmission among HSV partners. This was a reanalysis of an ineffective vaccine trial, alluded to by Hunter Handsfield and others earlier, in which over 500 monogamous heterosexual discordant couples were followed for 18 months. There was about six percent transmission, and condom use was reported as protective, interestingly, for women but not for men.

[Slide]

Now let's look at some of the data. If one asks how effective was the STD counseling provided in this study, what behavior change was actually found, as you see here, at baseline about 50 percent of couples said they never used condoms and in the month prior about a third said they nearly always used condoms. As mentioned earlier, when we calculate the nearly always used condoms during the study, it is based really on a median use of the eight months. So, if a couple reports five months using condoms all the time and then there is a month or two where they only use it sometimes or never, they still are classified as nearly always.

But if you look at the effects of counseling, as you can see, condom use during vaginal sex actually decreased slightly. "Nearly always" now is reported by 30 percent of couples, and a higher percent reported never using condoms. In oral sex, which was reported by over 70 percent of the partners, only seven percent in both groups reported nearly always using condoms for oral sex.

I must say, there is some difficulty interpreting the oral sex data because it is not clear in the reports in which direction the oral sex occurs. Is it man or woman, woman or man? So, it becomes difficult to know exactly what exposures, particularly during symptomatic periods, in one of the partners--whether risk or direct contact was made.

[Slide]

Looking at some of the behavioral data, as we have mentioned, the condom use collection or report can best be described as poorly defined. For oral sex I think was even more difficult to look at the data, particularly if one tries to then look at this issue of abstinence either of sexual behavior or specifically of oral sexual behavior during outbreaks. No analysis was conducted.

I am always struck as I read these studies of couples by what kind of data we collect and what we don't collect on couples. We collect data on duration and whether they have had a history of STD, but among heterosexual couples we don't have data like on marital status; whether people are living together; whether or not the couples have any children, which might give us some better definitions for being able to decipher who these couples are.

There was no analysis of the effects of counseling or, you know, how the data were collected on behaviors by different languages; how a number of these things were done considering the fact that it was multinational and multilingual, how different cultures might look at some of these definitions of oral sex or reporting different behaviors. Finally, there were a number of missing diaries.

[Slide]

In summary, I think we think the study was well done and does show that it does reduce clinical HSV-2 outbreaks among source partners and transmission to susceptible partners among these couples.

The viral shedding substudy I think clearly supports that valacyclovir does reduce transmission among such couples, and no new safety issues were identified to date in our review.

[Slide]

On the other hand, if one looks at the efficacy of the counseling and behavioral interventions, clearly subjects continued not to use condoms during every sex act, and very little during oral sex acts, and looking over the histories, there were individuals that did not abstain from sex during symptomatic recurrences despite counseling monthly. This behavior area may be an area that we can make some additional progress in, in addition to what we are finding with the medication.

[Slide]

With that, let me move on to the questions. I will just read them briefly. We will start out with one that, hopefully, will be fairly straightforward, does the information presented by the applicant support the use of valacyclovir to reduce the risk of transmission of genital herpes among monogamous heterosexual couples?

If you agree with that, we will them move

on to the other questions. If you don't, then we will talk about what additional studies need to be conducted.

[Slide]

After that one I think we get into some questions on how we are going to use this drug in practice and how we are going to fit it into public health guidelines. Does the information presented support the use of valacyclovir to reduce the risk of transmission of genital herpes among populations other than monogamous heterosexual couples?

[Slide]

Third is this issue of screening in 3009. Over 4,000 couples were screened. Only 1,500 were enrolled. Many of them, even though they didn't know they were infected, were. So, please discuss the implications of screening susceptible partners for herpes prior to initiating therapy of the source partner with valacyclovir.

[Slide]

Number four is a more philosophical question but one I know bothers some people in public health, what will marketing of valacyclovir for reduction of genital herpes have on the impact of use of condoms and following other STD

guidelines?

[Slide]

Fifth moves on to another issue which I guess deals with duration of therapy and resistance. Although patients in the registrational trial were treated for eight months, it is likely to be used for longer periods of time. What additional studies would you suggest to evaluate the potential for longer-term adverse events, including development of resistance to valacyclovir?

I guess I would kind of like to add a thought. When would you consider stopping to use this drug in a relationship? For example, what if the relationship breaks down? What if you get into another partner who is already infected? What if transmission occurs? If you get into a relationship and start this at age 20 and you stay in that relationship for 50, 60 years, how long should one continue the medication and should there be some monitoring, or whatever, in the process?

[Slide]

Finally the six question, getting back to this issue of the primary endpoint, in future studies for treatments for herpes simplex what do

you recommend that we use as a clinical endpoint? And, if we have time, which we probably won't, there is extra credit. One can try to address other STDs because I know we have other STDs that other manufacturers out there are interested in looking to see what impact this might have on HIV and other STDs.

So with that, I will conclude and turn it back over to Dr. Gulick.

DR. GULICK: You have one more slide, I bet you.

DR. HAVERKOS: Excuse me, I am sorry.

[Slide]

Dr. Smith and I would like to thank the collaborators and those who have provided us with all materials and told us what to say today. Thank you very much.

DR. GULICK: Thanks, Dr. Haverkos and Dr. Smith. Just a brief announcement, Dr. Handsfield mentioned that he would be willing to share his slides with people. He will post them on the FDA web site and he is also available if you want to get his e-mail address.

At this point we are going to go into a question and answer session. Although we just saw

the questions reviewed for the committee, I want to stress that we are going to focus on those during the afternoon period. The period now for questions and answers is really questions of content or clarification either for the sponsor or for the agency and their presentation. Dr. Kumar is jumping right in.

Questions from the Committee

DR. KUMAR: This is a question for the sponsor. If I understood the prevalence rate of herpes in African-Americans, it is about 47 percent, and if we just take African-American women it is about 55 percent. But the study, if you look at the population that was enrolled, only three percent were African-Americans. Could you comment on why that was and what did you, as the sponsor, do to encourage more participation of African-Americans?

DR. COCCHETTO: Sure, happy to comment on that. Let me ask Dr. Young to comment on that question.

DR. YOUNG: First of all, as noted in Dr. Harding's presentation, this study was conducted multinationally so we actually did have sites that were spread throughout the world. Now, we had

selected investigators that were in the U.S. as well as in Canada and actually did have access to diverse populations. Although I would acknowledge that we did enroll the percentages of African-American patients that you had identified, we had no restrictions on enrollment in terms of demographics. This is how the data actually played out. Those are the data.

DR. KUMAR: Dr. Young, about 860 patients came from the U.S. sites.

DR. YOUNG: That is correct.

DR. KUMAR: If I understood the data.

DR. YOUNG: That is correct.

DR. KUMAR: Can I just follow-up?

DR. GULICK: Yes.

DR. KUMAR: In the FDA briefing document there was some mention that some specimens were lost or contaminated. Would you comment on cultures from the European countries, from West Europe and East Europe? Could you give us a sense of how much of these specimens were lost or contaminated during transport here?

DR. COCCHETTO: Sure. We did look carefully at that issue of handling of specimens. Let me ask Stuart Harding to comment on that,

transport and our accountability for specimens.

DR. HARDING: Of those cases reviewed by the endpoints committee, 71 cases, there were six subjects in which there was a sample, or sometimes more than one sample that was missing or contaminated, or whatever. But when you consider that for a suspected cases samples are taken for culture and PCR on days one, five and ten and serology on day one and ten, and then there is continued follow-up with serology, we don't think that that would impact the results.

For your question about transport around the world and particularly from Europe, I am not aware that there was any problem with that transport. According to Dr. Ashley Morrow the samples typically arrived in very good condition and chilled. If you need more information I think she would be pleased to give you some.

DR. KUMAR: That is fine, I just wanted to get a feeling for that. Can I ask one last question?

DR. GULICK: Sure.

DR. KUMAR: Again, this is for the sponsor. Could you comment, on valacyclovir four patients developed herpes. Could you give me some

sense of their clinical presentation and how long was the follow-up that you had on those four patients?

DR. COCCHETTO: Let me just make sure I understand. You are asking for some clinical information on the four primary endpoints within the valacyclovir group?

DR. KUMAR: And how long they were followed.

DR. COCCHETTO: And how long they were followed. Again, I would ask Dr. Harding to comment.

DR. HARDING: I can't recall exactly but we do have the case narratives for each of those four, if you want us to show them.

DR. GULICK: Yes.

DR. HARDING: If we could have those? I can give you some summary details at least for the demography, and stuff. There were two male, two female, for example, ages 29-35, all from the U.S.

[Slide]

This is one of them. I don't know if you want me to read that or if you can read it from where you are.

DR. GULICK: Why don't you guide us

through it?

DR. HARDING: The randomized date was in October, 1999 and the date of the end clinical endpoint was June, 2000. The subject reported dysuria approximately four days before noticing a large erythematous papule on her external labia on June 13, 2000. On exam, four additional erythematous lesions were identified. There were confirmatory labs; culture taken on June 15th was positive.

[Slide]

Again, an American one, as we said. Randomization May 6, '98 and in August, end of August, subject returned to the clinic on September 2nd with a suspected genital herpes outbreak. Subject stated that prodromal symptoms started on August 31st, with lesions appearing on September 2nd. The office visit included tender palpable lymph nodes in the bilateral groin; fatigue, malaise and general rash. The confirmatory lab, culture and PCR on September 2nd were negative but the serology became atypical on October 13th and then converted fully to positive on December 2nd.

[Slide]

Another one, randomization in June, '98;

clinical endpoint December, '98. Subject returned to clinic on December 2nd with complaints of sore throat, genital tenderness and genital lesion that started on September 2nd. The confirmatory labs were both culture and PCR.

[Slide]

The last one was randomized April 21st. On April 29th the subject presented at clinic on May 1st, complaining of dysuria lasting two days. The labia was erythematous with no discrete lesions and extensive cervicitis. Culture and PCR were positive. In addition, serology on May 20th was positive. So, these are all fairly typical primary cases.

DR. KUMAR: Dr. Harding, I may not have asked my question clearly. What I wanted to know is not so much what the clinical presentation was but really what happened to them. Did they respond to a treatment? What were they treated with and did they respond? I recognize that you had not collected any resistance data. So, I was just trying clinically to see what happened to these four patients.

DR. HARDING: Well, they were all given one gram twice a day of valacyclovir for ten days.

But at that stage they were free to leave the study if we had the confirmatory labs.

DR. KUMAR: Can you give us a sense of whether they responded to the treatment that was given to them?

DR. HARDING: Can anyone help me as to whether we recorded that? I am getting shakes of the heads. This wasn't an analysis that we collected.

DR. GULICK: I guess what you are getting at is, just because of the issue of resistance, it would be nice to know if they responded to the therapy and healed the lesions.

DR. KUMAR: Yes, that is all that I wanted to know. Is there any sense of what happened once they got treated, and how quickly did they respond, and any such information.

DR. HARDING: Dr. Young has reminded me that all the isolates were susceptible but, of course, we didn't determine that until later. But we are not aware of transmission of resistant isolates in immunocompetent subjects anyway so I don't think this was a consideration.

DR. GULICK: So, the short story sounds like we don't have clinical information available

on that.

DR. HARDING: We don't have that sort of detail. Obviously, expecting very small numbers it wouldn't have really helped us over and above all the details we have on treatment of episodes.

DR. YOUNG: Just one additional comment, it is not unusual in our clinical studies on suppression to actually have individuals who may develop recurrences on active therapy. Typically, when these individuals are actually treated with what would be considered to be the standard doses they do resolve their lesions. So, it is really not an unusual circumstance.

DR. KUMAR: But we are not sure, Dr. Young.

DR. YOUNG: Not in this study. I am just making a general comment.

DR. KUMAR: We do recognize that but I think particularly for this group of patients that would have been important, with four patients that got it, it would have added a sense of comfort to clinicians like me.

DR. GULICK: Dr. DeGruttola and then Dr. Sherman.

DR. DEGRUTTOLA: I have a couple of

questions about the withdrawals first, directed first to the FDA but then also to the sponsor. As was correctly pointed out, the analyses are sensitive to assumptions about withdrawals so my first question is, is there any information about when these withdrawals took place? Obviously, for those toward the end of the study the assumptions have less impact on the analyses.

Also, was there any effort to find out more about who withdrew, not just the reasons for it but what the characteristics of people who withdrew were, and did those characteristics predict outcome and differ by treatment arm? Because that would be the case, again--where the characteristics predict outcome and differ by treatment arm--where the non-informative censoring assumptions would break down and could have an impact on the results.

So, two questions to start. Distribution, when they took place and who they were.

DR. SMITH: As far as when they took place, the applicant has, I believe, a Kaplan-Meier plot about the time to discontinuation in their package. Generally, it looked like--

DR. GULICK: Could you give us the page

number on that?

DR. SMITH: I can't give you the page number right away.

DR. GULICK: Anybody who has the page number could give it to us.

DR. COCCHETTO: Page 46.

DR. GULICK: Thanks.

DR. DEGRUTTOLA: So, it looks like it is pretty even over time, except right at the beginning.

DR. SMITH: Yes, so it looks like it is very even in terms of time to withdrawal, similar to the proportions analysis. Patients who had unknown outcomes in terms of the primary endpoint, they tended to withdraw earlier than other patients who discontinued. We didn't really get into that, you know, present, absent or unknown, as far as the primary endpoint was concerned but those patients who were unknown were counted--it was dichotomized; they were not counted as a separate category.

Basically, in terms of the types of withdrawals and withdrawal characteristics, I am not familiar with the withdrawal characteristics.

DR. GULICK: Does the sponsor want to comment on this?

DR. COCCHETTO: Yes. Dr. DeGruttola, we share your curiosity about the withdrawals, as well as Dr. Smith's, and we did look at those pretty carefully. If you put up D7, just so everyone can see the same graphic--

[Slide]

--that is the Kaplan-Meier plot. Let me ask Roger Liddle, who is the head of our statistics group for this trial, to make some comments to address your question, Dr. DeGruttola, from looking at patient characteristics as well as the time course of discontinuations.

DR. LIDDLE: Thanks. My name is Roger Liddle. I am vice president of biostatistics and data management for GlaxoSmithKline. Thanks for the opportunity to just take a few minutes to cover a couple of slides. Let me jump to D2.

[Slide]

We have covered already overall. We see a very similar discontinuation rate between the two treatment arms, with 22 percent on placebo and 21 percent on Valtrex. In the bottom part of the slide you see that over the course of time this is sort of similar, maybe just a quick summary to the slide you have already seen but if you look at the

three-month period, less than three months, three to six or more than six, there was somewhat of a tendency to withdraw earlier from the study, but between the two treatment groups the pattern was very consistent. Let's go to D3, please.

[Slide]

I think with respect to that, what is the impact and what are the various analyses, and how dependent are they on the different analysis methods? The key sensitivity analyses that we performed, one was time to event which certainly has some appeal because we get to use the data right up until the time of discontinuation. With the as-treated analysis, we really focused on those patients who completed the entire study. The imputation approach, which was also referenced in the FDA presentation--here, what we have chosen to do rather than say 100 percent or five percent or whatever else the discontinuations, here what we did was we took the placebo rate for transmission and we applied that rate to the discontinuations. So, if we saw something between two and three percent on the placebo arm, that would correspond to four or five additional events. So, we added those four or five additional events to each

treatment group. So, we sort of imputed the placebo transmission rate for each of the treatment arms.

In all three of those cases, the intent-to-treat, the as-treated, the time to event and that imputation, in all three cases the statistical test was robust for those and we did see a significant, less than 0.05, p value in all three of those cases. Let's go quickly, if we can, to D9.

[Slide]

These are the p values that I just referenced. You see the primary analysis was the 0.011 which has been referenced a couple of times this morning. Time to event is the 0.008. Perhaps not surprising, because we are using all the data it does give you a bit more power. The as-treated analysis was 0.012. If you use that placebo rate, it came out as somewhere between four and five events. So, we have shown the results both for four and five events added to the two treatment groups.

In a sense, this itself is being a little bit conservative because we have ignored in this imputation approach the fact that we do have some

data for those patients. They did not get the transmission and we have actually imputed the placebo rate as if it was the entire eight months. If you actually said, well, they were on average in the study for three months and used a sort of time-dependent transmission rate it would be more like three events. So, again, it would still be significant. So, in this sense it is perfectly appropriate to look at a variety of the sensitivity analyses but in this case they were all robust to that.

I think the question about was there information in those discontinuations, I have one additional slide I would like you to talk you through very briefly, slide D27.

[Slide]

This is actually fairly recent work. We, obviously, were still trying to understand if there was information in these discontinuations. What we have done is we took a variety of baseline characteristics that are listed over on the left-hand side of this, and we have looked at them to see if they were predictive of discontinuation. There, what you will see is that the first five were not predictive of discontinuation and,

therefore, would not likely drive some bias because of the discontinuations. So, we sort of didn't worry about those.

The four at the bottom were of some concern but then, of course, the next question is are they predictive of primary outcome? If they are unrelated to the primary outcome, and the HSV-1 for the susceptible partner was not predictive of the primary outcome, again we don't see that as a concern.

That still leaves us with three baseline characteristics that were potentially of interest and could conceivably result in some bias in the results. For two of those, the country where we analyzed it as U.S. versus noon-U.S., and the duration of relationship--as I said, they were somewhat related to discontinuation and they were somewhat predictive of the primary outcome, with U.S. being more likely to transmit and shorter relationships being more likely to transmit but, in fact, there was not evidence of a differential rate in the discontinuation. So, while that may have had some effect on the overall transmission rate, it should not have a bias in favor or against one treatment arm versus the other.

That leaves us really with one variable which was potentially of interest and could have had some bias. That was the duration of the HSV-2 in the source partner. But in this case it is interesting to note that because Valtrex was associated--sorry, let me get this straight--this does imply a potential bias against Valtrex and for placebo. The reason for that is that HSV-2 infection is correlated with clinical acquisition. The duration of the HSV-2 infection is correlated with clinical acquisition and is also correlated with a higher discontinuation rate for the placebo arm. So, if in fact that baseline characteristic, if there is information there, it means that placebo patients were a bit more likely to drop out and were more likely to have been transmitters. Therefore, at least based on this analysis that we went through in some detail, we felt there were no red flags or cause for concern based on a fairly comprehensive look at baseline characteristics. Thank you for your patience.

DR. DEGRUTTOLA: Thank you very much, that was very helpful and very useful. I have a couple more questions. One is to the agency, given the fact that, as Dr. Liddle just mentioned, at least

in the Kaplan-Meier analysis you can use the information up until the time the subject discontinues, why were the primary analyses that you presented based on odds ratios rather than the time to event analyses, and could you comment on the appropriateness of the time to event analyses, given that in some cases--I think in all cases there was a higher degree of statistical significance, not greatly but it was greater?

DR. SMITH: We found that the Kaplan-Meier analysis was slightly more powerful but we didn't find a tremendous deal of difference between the two approaches and since the primary analysis was done on the proportions we just tried to look at the proportions that correspond to the primary analysis. But we would expect similar sensitivity for the Kaplan-Meier analysis if you counted withdrawals randomly.

The other problem with the Kaplan-Meier analysis is it depends on which withdrawals from, say, the five percent you choose as failures.

DR. GULICK: Can you speak up a little bit?

DR. SMITH: Sorry. If you choose five percent of the discontinuations and treat them as

failures, then you have a little bit of a problem where they are all going to have different failure times. So, it depends on which ones you randomly choose.

DR. DEGRUTTOLA: I agree, if you were going to do sensitivity analyses you might want to make different kinds of assumptions, or would have to make different kinds of assumptions. But it sounds as if in general you considered the Kaplan-Meier analyses appropriate and informative even though all of them have issues with withdrawals.

Dr. Smith presented analyses showing that there was a significant geographic effect on the risk of developing the endpoint. But was there was there an analysis done of the impact of geographic region on the treatment effect?

DR. SMITH: Yes, we did analyses looking at treatment by geographic region interactions. In that case we didn't find any statistical significance so it was mainly the main effect of geographic region regardless of which treatment they were on.

DR. DEGRUTTOLA: And one final question just to clarify, for the primary analyses patients

were followed after drug discontinuation and included in analyses and then intent-to-treat ways. Is that correct?

DR. SMITH: Patients were followed for eight months, the duration of the double-blind study. After that we didn't look at events after eight months because all the patients were put on open-label treatment.

DR. DEGRUTTOLA: But if there were treatment discontinuations prior to eight months, were those patients no longer followed?

DR. SMITH: They were no longer followed, to my recollection, after they discontinued from the study.

DR. DEGRUTTOLA: Could they discontinue--maybe this is a question for the sponsor, could patients discontinue treatment but continue to be followed in the study? Or, once they discontinued treatment was follow-up discontinued?

DR. HARDING: Obviously, the typical case was when they discontinued they were not followed. There was a small number of subjects who did remain with follow-up. In fact, we tried to get serology after discontinuation where possible.

DR. DEGRUTTOLA: And is that true for partners as well, if they changed partners or treatments that they were no longer followed?

DR. HARDING: If the susceptible partner changed partners, yes, there were some instances where they continued but, according to the protocol, they should have discontinued because they are no longer monogamous.

DR. GULICK: Dr. Sherman and Dr. Fish.

DR. SHERMAN: Thanks you. Two points of information just to help clarify some things for myself, for the sponsor, can you explain why in your design you limited the number of episodes permitted per year to nine or less?

DR. COCCHETTO: Sure. The regimen of Valtrex evaluated in this trial is currently approved for suppressive therapy for patients with nine or fewer recurrences per year. So, in order to be able to compare a single regimen of Valtrex versus placebo we focused on that group of patients.

DR. SHERMAN: Wouldn't you have had a somewhat higher yield in patients that presumably shed higher levels of virus?

DR. COCCHETTO: Let me ask Dr. Harding to

comment on the proportion of patients who have those particular histories of recurrences.

DR. HARDING: As I said in my presentation, the vast majority, about eight percent of subjects, do have nine or fewer recurrences so this was the predominant population. But we did have two other considerations as to why we didn't choose people with ten or more recurrences. One was the fact that they would be more likely to actually want treatment as opposed to have the possibility of placebo so it was bordering on whether this was ethical. The other is that if they had such frequent recurrences they may be more easily able to discern whether they were on active or placebo and, therefore, break the blind because it would be pretty obvious if they started taking Valtrex.

DR. SHERMAN: Okay. The second question relates to actually one of the slides that Dr. Handsfield showed in his discussion of the sexual dead zone after about age 40. If the rate of transmission is about 2.5-3.0 percent per year in untreated patients, how come we don't see in stable monogamous couples continued effect of infection on and on and on because it is going to take many,

many years, 30 years or more, at that rate to continue to completely infect the stable partner population? This question is relevant to how long does one ultimately continue treatment. Is there a time period where pretty much the risk of transmission ends?

DR. HANDSFIELD: I am not sure we know definitive answers to those questions. I have given you the clues that one might suspect that subclinical shedding because symptomatic recurrences probably wane over long periods of time, after several years, and it is a fair assumption that subclinical shedding may as well. So, a longer duration relationship may become less risky from that standpoint over time. That is hypothetical; it hasn't been sufficiently studied.

There has also been speculation, and Dr. Corey or others can answer this part better than I can, about whether there might be some level of non-measurable immunity, that is, not measured by current approaches to antibody levels or perhaps even cell-mediated immunity, but, nevertheless, as has been analogous and suspected for some HIV cases, low level exposures might, in fact, result in some level of protection that is not detectable

by those methods, which also might be expected to have its effect in couples over time. So the exact physiologic explanation for the epidemiologic observations I think is not something we have definitive answers for, but that is my epidemiologist's response but perhaps others have comments on it.

DR. SHERMAN: But would it be fair to say, and perhaps a representative of the sponsor can answer this, that at some point it doesn't appear that suppressive treatment may, in fact, be indicated?

DR. HANDSFIELD: I will comment, if I can continue, and then I will sit down. I think that begins to get to issues that are not yet on the table but clearly will be, and that is, what are some of the extrapolations that can or should be made from a public health standpoint? The notion that viral shedding is the most common in the first months to a year or two after acquisition, therefore, differential benefit might be seen in people with shorter-term relationships and/or more recent acquisitions I think is certainly the implication of what you are asking and I think that is potentially a valid implication. That doesn't,

however, undermine the high value, regardless of the public health benefits, in those individuals who have ongoing relationships who are looking for that level of assurance or protection that they may want over a long period of time.

DR. GULICK: Let me caution us not to get into the discussion period just yet and let's stick to questions of clarification at this time. We have plenty of time to grapple with some of the questions a little bit later on. Dr. Corey, do you want to add something?

DR. COREY: If I might comment, it is a great question but, you know, you are asking about an area in any infectious disease and especially for genital herpes and we actually don't know a lot of information about the exact issues of transmission. As an anecdotal case, both in the Chiron study and this study, we have had people who have had in monogamous relationships for greater than eight years and ten years who actually transmitted on study at that period of time. So, for a long duration. Yet, when you look at relative risk factors, certainly shortness of the relationship increases the relative risk by, let's say, a factor of 2.5 to 3. And, duration of

genital herpes, long duration, decreases the risk factors.

Now, how much of that is due to biological factors that relate to frequency of subclinical shedding that decreases over time; how much of it relates to behavioral factors that are associated with sexual practices that go with duration of relationships, and how much is the other new factor which is essentially innate resistance, just like in HIV where there has been among high exposed seronegative men and women T-cell immunity associated with no seroconversion? Chris Posavad, from our group, has recently reported that now with some HSV seronegatives.

So, on a population basis we have a complex interplay here that we actually can't really play out in a definitive way from a counseling point of view, unfortunately, at least in my opinion.

DR. GULICK: Additional questions of clarification? Dr. Fish and then Dr. Englund.

DR. FISH: I have three questions, if I may. Understanding that the primary endpoint related to genital HSV-2, and on slide 28 you mentioned it was culture, PCR or serology that was

utilized, I thought I heard the sponsor say that there were no cases of HSV-1. Is that correct?

DR. COCCHETTO: That is correct.

DR. FISH: And how is that known?

DR. GULICK: Sorry, we need people to go to the mike to answer.

DR. HARDING: There were no primary acquisitions of HSV-1 genital herpes in the susceptible partners. There were four asymptomatic seroconversions. Does that answer the question?

DR. FISH: So, no clinical endpoints but four seroconversions to HSV?

DR. HARDING: Yes. The serodiscordancy for HSV-1 was only 13 percent where, of course, it was 100 percent for HSV-2. So, although nowadays a fair number of primary acquisitions of genital herpes are HSV-1, I think because the gradient, if you like, was much smaller in our study we didn't actually have one but we did look for it.

DR. GULICK: Can people hear in the back of the room? All speakers, please speak loudly and into the mikes.

DR. FISH: The second question relates to the counseling design. Was there a specific script given to the investigators in terms of counseling

about condom use, or was this left to investigator discretion?

DR. HARDING: There was no specific script. They all had the American Medical Association booklet, which was state-of-the art at that time, 1997. They were instructed in the protocol and at investigator meetings to make sure that people could recognize the signs and symptoms because that obviously is a big feature, and then the abstinence and the condom use. The fact that counseling was given was checked off in the CRF so at each visit they had to verify that they had done that.

DR. FISH: Thank you. Then a last question for the agency, there were approximately 25 percent fewer primary endpoints than anticipated, 20/28 that they thought one might see in the 1500 who were entered. Can you comment in terms of how this might affect, if at all, the robustness of the analysis?

DR. SMITH: Well, given more endpoints, the analysis, had there been the same difference between the two treatment groups, would have been more robust to discontinuations because there were so many more discontinuations than endpoints. That

is why we had a lot of trouble with the sensitivity because of the fact that the discontinuations just swamped the treatment effect.

DR. GULICK: Dr. Englund?

DR. ENGLUND: I have some questions about the seroconversions as the secondary endpoint, and specifically on slide A44 for the sponsor, because in fact serology was an entry point for the study, I am interested in these 36 seroconversions as a secondary endpoint. Did those include the patients that were culture and/or PCR positive that were serology negative at the time, perhaps of a timing issue? In other words, do the seroconversions include all those that had symptomatic clinical disease documented by other laboratory parameters?

DR. HARDING: Perhaps if we have slide A44 it would be helpful.

[Slide]

So, you have your 36 seroconversions and, as you see, 15 were from the primary endpoint. The culture or PCR came first but seroconversion was detected later. For the five that were determined to be endpoint based on culture or PCR, three of them left the study there and then and there was no adequate duration of follow-up for seroconversion

but, obviously, we would have expected them to convert given time. Then, there were the three seropositives from the cases referred to the endpoints but without culture or PCR positives.

So, the overall acquisitions is probably the best endpoint to look at as a secondary endpoint compared with the primary because that now includes the cultures or PCRs taken at the time. It wasn't that patients were always followed for long enough to ascertain seroconversion. Does that answer your question?

DR. ENGLUND: Well, it does because one of the questions when you are looking at the secondary endpoint is that you want to make sure that you aren't missing any, and you are saying you probably aren't but you don't have the data on several patients.

DR. HARDING: That is why I included the overall acquisitions because that includes not only the seroconversions but those for which we have culture and PCR. If you just look at seroconversions, you may have missed some who withdrew from the study having had a positive culture.

DR. ENGLUND: I have another question in

which perhaps you might be interested. This is regarding resistance and I would just like to ask perhaps one of our other experts here, but to my knowledge there has never been resistant HSV transmitted from an immunocompetent person to another immunocompetent person, whether it is HSV-1 or HSV-2. Is that correct?

DR. HARDING: That is my understanding.

DR. GULICK: Dr. Mathews?

DR. MATHEWS: I wanted to return briefly to the issue that Dr. DeGruttola raised about whether there was a differential dropout because there were a couple of other risk factors that I didn't see on the slide that probably are relevant, and those are whether the dropout was differential by condom use, either at baseline or on study, and also by the reported frequency of intercourse. Do you have any analyses that looked at those factors?

DR. COCCHETTO: I am looking to my colleagues to see if one of them can help us with that. Roger?

DR. LIDDLE: I may be able to answer but it won't be totally satisfying. I think in the analysis that I presented we were looking at baseline characteristics. We were trying to

understand what differences in the patient population when they walked in the door could drive some bias induced both by the differential dropout rate and some effect on overall acquisition. So, we were not looking at variables that we were monitoring during the study, such as the condom use during the study or the frequency of sexual activity during the study.

DR. MATHEWS: Well, you probably have the data, right? I mean, the effect size for condom use in one of the analyses you presented was a relative risk reduction of about 0.5 so it is not a trivial protective factor. So, I would suggest those be looked at by the agency as well as the sponsor.

Secondly, dealing with the point Dr. Sherman made about how long the period of risk might last, you might have some data in this trial by looking at what happened to the effect size for the treatment by antecedent duration of the partnership, recognizing that there were not a lot of endpoints but if you even made one cut point in the duration of the partnership was there modification of the magnitude of the effect?

DR. LIDDLE: We did look at the duration

of the relationship and there was some impact. The shorter duration of relationship was associated with an increased chance of discontinuation and was associated with an increased chance of our primary outcome of transmission.

DR. MATHEWS: So, if you were to estimate the relative risk reduction for those who had, say, partnerships of two years or greater versus less than two years, those kinds of analyses, was there evidence of an effect size difference?

DR. LIDDLE: We did not calculate relative risk factors so I actually can't comment on how big a difference that was. There was somewhat of a relationship; I don't think it was huge. Can anybody help me with that?

DR. COCCHETTO: Dr. Wald is pressing to comment.

DR. GULICK: Please state your name and your affiliation.

DR. WALD: Anna Wald, University of Washington. Although short duration of relationship was a risk factor for HSV-2 acquisition in this study, there was no interaction between the valacyclovir effect and the short duration of relationship.

DR. LIDDLE: This is Roger Liddle again, if I can just follow-up, I think the relative risk was a factor of about 2.5 so it was a fairly significant change, duration of relationship related to acquisition rate, the relative risk was a factor of 2.5.

DR. MATHEWS: I would suspect you didn't have a large power to detect an interaction given the number of events.

DR. LIDDLE: I am sure that is true.

DR. MATHEWS: One last question relates to the condom use. Dr. Haverkos showed us cross-sectional data on the frequency of reported condom use before starting the study and on study. It might be helpful to know cross tabulation. For example, the people who were never using condoms before the study, what proportion of them started using them? The analyses you showed were just cross-sectional and didn't show a lot of change, but was there mobility when you look within subjects across time?

DR. SMITH: I think we looked at that and we didn't see that much of a difference. I can't remember if we have it on a backup slide but we could maybe look for that, if we have it.

DR. MATHEWS: This will come up later in the discussion but if, in a setting like this where there was a conscious intent to educate and encourage condom use, you really don't see any effect it raises questions about, if the indication is granted, how effective any educational programs along with it will be.

DR. GULICK: Let's hold that thought for the discussion but that is an important point.

DR. COCCHETTO: Can I add something to that?

DR. GULICK: Let's actually not add anything at this point in the interest of time. This is one of the questions we will be facing in the afternoon so let's not.

DR. COCCHETTO: Let me just say we have looked at those data.

DR. GULICK: Okay, thanks. Dr. Potter?

DR. POTTER: Yes, actually I was concerned about the fact that there were 4,000 people, there were attempts to recruit 4,000 with 1,500 actually included. It was mentioned that for most of them it was because the partner was already seropositive. But I wanted to know about the rest of that group. You know, what proportion was

because they were already seropositive? What were the reasons for refusal? Because this would reflect the typical user as opposed to the more perfect user that takes part in a study like this.

DR. GULICK: So, the causes of screen failures, the proportions?

DR. POTTER: Yes.

DR. HARDING: What I said was that the most common reason was the lack of serodiscordancy. In fact, overall it was about 30, 34 percent so it wasn't the majority. As the study went on and recruitment got more difficult, more advertising was done and people came forward, thinking that they might want to participate in the study or they might just want a free serology test. So, there was about another 20 percent and the source partner was not confirmed to have HSV-2 by serology. That has not accounted for about 54 percent of the subjects. I think there was another big chunk, probably about 30 percent, who, when they found out what was required of this study with all this personal, intrusive stuff and the duration of the study, they refused to participate. In fact, there were three sorts of major reasons, not just lack of discordance.

DR. POTTER: My real question was about that last group. If they were the people who would have had more trouble complying with the regimen, you wouldn't have data on that I guess. And, the same thing happens later--I am not sure of the direct link here but track of compliance with the Valtrex itself during the course of the study. In other words, if people refused to participate, was there a proportion that refused because they thought they couldn't follow the regimen that carefully and then, during the study was there track of compliance to see how forgiving the method is? Does that make any sense?

DR. GULICK: Dr. Cocchetto?

DR. COCCHETTO: I think so. You can help me further. On the first part of your question, at the point of screening where couples were considering the trial they considered the entirety of the trial. So, they would include consideration of their ability to adhere over an eight-month, double-blind period to study medication, as well as the need for monthly follow-up visits, laboratory specimens and so on. We don't have specific data on which component of that drove their decision-making. Anecdotally, as Dr. Harding has

said, the personal intrusiveness seems to be the dominant factor pre-study. During the study we did use a straightforward table count methodology to track medication compliance and we could share that with you perhaps this afternoon.

DR. POTTER: Thank you.

DR. GULICK: Yes, Dr. Guinan?

DR. GUINAN: Thank you. I would like to see gender stratification breakdown on the substudy on viral shedding and the results. Thank you.

DR. GULICK: Was that clear?

DR. HARDING: We have not done that analysis as yet.

DR. GULICK: Other members of the committee who haven't had a chance to ask questions who would like to? Dr. Fletcher?

DR. FLETCHER: I have two that I think are quick. First, the say, at least in the sponsor's briefing booklet, that amendment IV is presented, it says the sample size was revised in order to observe 28 confirmed endpoints. As I read it, and I think this kind of follows Dr. Fisher's comment, I was expecting to see 28 endpoints and there are not. So, was there agreement between the sponsor and the agency that there did not have to be 28

endpoints?

DR. HARDING: Yes, the protocol started off with 1,500 but actually, strictly speaking statistically, it is the endpoints that matter and, therefore, I think the protocol was amended to reflect that degree of finesse. What happened in practice was we were having considerable difficulty enrolling subjects, as you have heard, and then in May of 2001 we had achieved 23 possible endpoints because, obviously, there was ongoing review as faxes came in, information and so on. So, giving the sites sort of six weeks to complete their period between screening and enrollment, and then another eight months for subjects we reckoned we would probably achieve over that sort of ten-month period another five endpoints because that was our estimated rate, and it turned out that we had about 1,500 couples; we anticipated 28 endpoints but we didn't achieve them.

DR. FLETCHER: Then my second question, again just to make sure I am clear, what the sponsor is requesting on the dosing is no statement regarding duration so 500 mg once daily but nothing on the duration of therapy. Is that correct?

DR. COCCHETTO: In our proposed labeling

for duration it is quite explicit about the nature of the 3009 study in stating that the study was conducted for an eight-month, double-blind period. We have also proposed a statement elsewhere in the labeling to be clear that efficacy beyond that eight-month duration has not been demonstrated.

DR. GULICK: Are there other members of the committee who haven't had a chance to ask questions--I will come back to you, Dr. Guinan--who would like to ask questions?

[No response]

I have a few and then I will come back to you. One of my questions concerns the endpoint committee. I am trying to get a feeling for actually how the cases were evaluated in terms of what was available to the endpoint committee--history, pictures, what kinds of things were looked at?

DR. COCCHETTO: We are fortunate to have Dr. Corey here who chaired the endpoint committee. I will ask Dr. Corey to comment.

DR. GULICK: Great!

DR. COREY: As Dr. Harding said, there was both real-time monitoring and then a formal evaluation at the end of the endpoint committee.

The charts were all reviewed for any clinical signs and symptoms of genital herpes. All the laboratory data from the cultures and PCRs were made available and a serial line listing on each individual case was given on the serologies. So, the endpoint committee did all these evaluations in a blinded fashion. The definitions, of course, were agreed upon prior to the onset of the study. We actually reviewed the definitions before our formal endpoint meeting and agreed there would be laboratory confirmation that would be critical, essentially necessary to require a case, and the focus was were the signs and symptoms compatible with genital herpes from the narrative as it relates to the finding? Was it conceivable that these signs and symptoms were related to the laboratory confirmation of the test?

Of all the endpoints, actually there was really 100 percent unanimity on the endpoint committee on all except one endpoint, which we ended up classifying as an asymptomatic acquisition in a case that clearly had HSV-2 seroconversion, had some very vague symptoms and signs that were related to the general area that were prolonged itching that the majority of the members felt could

not be associated convincingly enough at the time of the signs and symptoms with the seroconversion to be called a clinical endpoint. It certainly was a total overall acquisition. That was the only endpoint that had any dispute or difference among the six members of the endpoint committee.

DR. GULICK: Just so I understand, the investigator would do a clinical evaluation; write up a history of what went on; serologic testing would be done; and then the endpoint committee would receive--

DR. COREY: That, as well as the fact that there was 100 percent monitoring by the sponsor on those narratives. So, the narratives were really confirmed not only by the investigator but by the monitoring. They were written up and the narratives were made available with all the laboratory testing, as well as what the clinician diagnosed and whether medication was dispensed for an incident case.

DR. GULICK: As I understand, of the 51 endpoints that were rejected, in all but three it was because the serologic test was negative?

DR. COREY: Correct.

DR. GULICK: We heard about the other

three and why they were different.

DR. COREY: Correct.

DR. GULICK: Thanks. My next question is about resistance. Did I understand correctly that ten viral isolates were available to be tested for resistance? Yes.

DR. GULICK: So, it was from the source patient obviously, and that is pretty much the extent of the resistance information that is available?

DR. COCCHETTO: Well, let's clarify that further. Dr. Harding, do you want to comment on those ten specifically?

DR. HARDING: There were ten cultures from the susceptible--

DR. GULICK: Susceptible?

DR. HARDING: And one from Canada which is currently being tested for resistance.

DR. GULICK: And no evidence of resistance in any of those cases?

DR. HARDING: Not at all.

DR. GULICK: Then, one question for the agency. Reading through the background material, apparently the agency initially suggested that two studies would be preferred. What we have seen here

is one large study. I wonder if you could comment on the discrepancy between those two recommendations.

DR. BIRNKRANT: I believe the original recommendation for more than one study was to be able to capture a more diverse patient population, and it was left to the applicant to decide whether to do one or two trials.

DR. GULICK: Thanks. Dr. Guinan, I am going to go back to you. I bet I got your question, didn't I? Anyone else who hasn't had a chance to ask a question? Dr. Stanley, I have forgotten you.

DR. STANLEY: No, you all have clarified all the questions I had.

DR. GULICK: Super! We will have additional time for questions in the afternoon. At this point I would like to go to the open public hearing part of the agenda. We have four people who have signed up previously to speak at the open public hearing, actually five. The first one is Dr. James Allen who is from the American Social Health Association.

Open Public Hearing

DR. ALLEN: Thank you, Mr. Chairman. I am

James Allen, President and CEO for the American Social Health Association, also known as ASHA. We appreciate the opportunity to comment on approval of valacyclovir suppressive therapy to reduce the risk of transmission of genital herpes. ASHA is a nonprofit organization that has focused on education and prevention of sexually transmitted diseases since 1914.

We have operated a National Herpes Resource Center for the last 24 years. Through this center and our associated services, such as the National Herpes Hotline, the National STD Hotline, Internet-based services, local support groups and involvement with an international patient advocacy movement, we interact with tens of thousands of people affected by herpes every year. Because of this background and the work that we do, ASHA would like to address the issue of preventive antiviral therapy to reduce the risk of transmission of genital herpes from a patient advocacy perspective.

Our comments today reflect our strong history of patient advocacy and the information and concerns we have gleaned from contact with people living with herpes. ASHA fully supports approval

of the GlaxoSmithKline application for valacyclovir suppressive therapy in reducing the risk of transmission of genital herpes.

As a prelude to this statement, ASHA discloses that we have received charitable grants from GlaxoSmithKline, as well as from other pharmaceutical companies, to support our herpes educational activities and resources. These monies have been provided for specific activities to be conducted by ASHA such as operation of the Hotline or Resource Center or convening of a scientific meeting, but we have not used these funds for promotion, either directly or indirectly, of products or services related to the pharmaceutical companies providing this support. The message and information provided by ASHA are determined by an independent scientific and medical review and are not related in any way to funding from specific manufacturers.

One of the most prominent concerns expressed repeatedly to ASHA by people with genital herpes and their uninfected partners is the risk of transmission. Quite apart from the physical aspects of recurring signs and symptoms, genital herpes can create continuing anxiety and

psychological distress. From a patient perspective, it is extremely difficult to adjust to the uncertainty of this infection--the fact that one might be infectious to others even at times when no signs or symptoms are present. Affected people and their partners want to know what they can do, what preventive steps they can take. Unfortunately, the options for reducing risk have been limited. An effective vaccine for the herpes simplex virus does not exist and prevention alternatives for this chronic, lifelong infection are not perfect or reliable.

ASHA encourages infected persons and their partners to consider any and all of the options available. We advice infected people to disclose this information to their partner, to have open communication and discussions, and to abstain from sexual contact if symptoms or signs of infection are present. Each of these has an important place in the prevention message. ASHA promotes consistent and proper condom use as well, with the important caveats that condoms should not be relied upon during symptomatic periods and that condoms are never 100 percent effective.

Clearly, however, more choices are needed.

People with genital herpes have long wanted to know whether antiviral medications would be helpful in reducing risk of transplantation, and for years we have informed them we have no data. The results of the herpes suppression transplantation study, which you have heard today and that was presented by Dr. Lawrence Corey of the University of Washington at the Interscience Conference on Antimicrobial Agents and Chemotherapy in September, 2002, however, provide convincing evidence that suppressive therapy is effective at reducing both the frequency of clinical recurrences and the risk of transmission of infection to an uninfected partner. This information significantly substantiates the claim that reducing the risk of herpes transmission should be a labeled indication for valacyclovir. Such a step will give physicians and people with genital herpes another option to consider as a risk reduction method.

In conclusion, ASHA believes that people with genital herpes and their partners should have more information about risk reduction options, beginning with the counseling they receive from their healthcare providers, and they need more choices to consider when faced with the need to

reduce to a minimum any risk of transplantation of herpes infection to a partner. Given the information currently available, ASHA urges the Food and Drug Administration to approve the GlaxoSmithKline application for valacyclovir as suppressive therapy to reduce the risk of transplantation of genital herpes. Thank you.

DR. GULICK: Thank you very much. Next is Mr. Gray Davis who is Director of the HIV Prevention Trials Network. Oh, I am sorry, that is clearly a grave error, Ms. Gray Davis, Dr. Gray Davis. Thank you.

DR. DAVIS: You will get it right soon!

DR. GULICK: Thank you.

DR. DAVIS: I guess we have established that my name is Gray Davis and I am the Director of HIV Prevention Trials for Family Health International. I am here today not as a representative of any organization but as a private citizen with a background in the field.

GlaxoSmithKline did not ask me to come, nor are they supporting my attendance in any way, nor were they informed that I would be here. In the past I worked for Burroughs Welcome Company and then for Glaxo Welcome as the international project

leader for acyclovir, which is the parent compound to valacyclovir.

I am here to talk about the importance of prevention. Managing an epidemic requires more than just having an effective treatment for outbreaks. It requires prevention interventions, diagnostic tools and counseling techniques. Given that at least 11 million people got infected with HSV-2 between 1980 and 1990, and since little has changed in the way we manage this disease, we are likely to see another 15 million people infected between 1990 and 2000. This is of particular concern since, as with other STDs, women are more severely affected and bear the burden of some of the more devastating outcomes of genital herpes.

Today we have an opportunity to have a major impact on the transmission of this infection. By approving Valtrex for prevention of transmission you will give clinicians one of the much needed tools to combat this disease. Provision of an effective prevention strategy will empower people, especially women, to make decisions and take control of their lives. Women can encourage their partners to wear condoms but they can't always enforce that. This will be an intervention with

equal opportunity for everyone.

The availability of Valtrex will substantially enhance the provider options on how to control this disease. The very act of writing a prescription will provide a window of opportunity for counseling. Patients can be encouraged to talk to their partners, to use condoms, to avoid sex during an outbreak, and to take daily therapy. Each of these strategies are complementary and provide additional tools in the toolbox for prevention. None should be considered exclusive of the others.

Why has genital herpes gotten so out of control? Perhaps because it is an STD we are uncomfortable talking about it. Both clinicians and patients may be reluctant to bring up the subject because society has labeled people with STDs as somehow dirty, or stupid, or deserving of what they got. Why would you want to talk about something like that?

Clinicians have said that the reason they didn't want to bring up the subject of herpes was because they knew the patient would get upset about it; they didn't know what to tell the patient; and they weren't confident of the test. After all, 50

percent of the time cultures are falsely negative. Once diagnosed, there wasn't much they could do for the patient anyway. So, rather than bring up the subject, they elected not to talk about it. Why tell the patient that they have a disease they don't know they have? However, how can you control an epidemic if 80-90 percent of the people who are infected don't know that they are infected?

Today we have many of the needed interventions to reduce the spread of this infection. Reliable, accurate diagnostic tests that can identify infected individuals are now available. Clinicians can accurately diagnose patients in their office using a diagnostic test as well as by drawing blood to send to a central lab for both diagnosis of HSV-1 or HSV-2. Thus, accurate diagnostic tests are now available to everyone.

We also know what to say once a patient is diagnosed. Hotlines, written materials and web sites are available to both clinicians and patients to help them understand the disease and to provide accurate, non-judgmental information. As you heard earlier from Dr. Allen, the American Social Health Association has a hotline available five days a

week from 9:00 a.m. to 7:00 p.m. This hotline is free of charge and is an excellent resource for both clinicians and for people with herpes. Clinicians can now refer their patients who need more lengthy consultation to a reliable source for information, and patients have a place to call for anonymous accurate information. The counselors at ASHA will spend as much time as needed to provide the best support for the caller. Written materials provided by ASHA and other organizations are also available.

Lastly, information is available on the web for anyone who wants to know more about this disease. The American Herpes Foundation and the American Medical Association have information and CME courses for clinicians. Another site, herpesdiagnosis.com, provides information for both clinicians and patients on how to diagnose and manage this disease. It also provides check lists for the clinicians regarding what to tell the patient, and for the patient regarding what questions to ask the clinician.

So, now we can accurately diagnose this infection and we can accurately provide counseling to the patient. The next step is to provide a

therapeutic intervention. The availability of Valtrex for reduction in transmission enhances our armamentarium for the control of this disease. As stated earlier, it is just another tool in the clinician's toolbox. We can now accurately identify those infected. We can educate about the natural history of the disease. We can teach patients to recognize recurrences. We can help them find ways to talk to their partners. We can instruct them to wear condoms, and we can offer an easy daily therapy to reduce transmission.

Whenever the FDA is asked to approve a drug they have to weigh the benefits of therapy against the potential toxicities. Rarely is there a case in which the benefits of therapy so far outweigh the potential risks. Valtrex has an impressive safety profile which makes your decision today much easier. You can concentrate on whether or not the benefits of this medication warrant its approval.

Some decision-makers seem to think that herpes is a benign infection with no severe sequelae. However, as with much of the history of herpes infections, the more we know about this disease the more we are surprised to find out how

our beliefs are wrong. Neonatal herpes affects one in 3,000 births in the United States. That is about four babies a day. The best way to prevent neonatal herpes is by preventing the mother from becoming infected in the first place.

As Dr. Handsfield presented earlier this morning, there is also the link with both transmission and acquisition of HIV. If we have learned anything from our African friends, it should be the lessons learned from herpes. In countries most severely affected by HIV, the herpes epidemic predated the emergence of HIV. In each of the countries in which we know the seroprevalence of herpes infections, the higher the seroprevalence of HSV, the higher the seroprevalence of HIV. Needless to say, we need to do everything within our means to prevent these infections.

Finally, the investigators, the company and, most importantly, the patient should be commended for undertaking this trial. I am currently trying to do similar prevention trials for HIV. It is extremely difficult to get patients to participate in transmission studies. Identifying discordant couples and getting them to agree to participate in a placebo-controlled trial

is a challenge. People are uncomfortable acknowledging that their relationship has placed them at risk of acquiring a sexually transmitted disease. Many people, while being aware of the risk on a certain level, have a hard time acknowledging it by actually participating in a trial. Other patients, when hearing the rationale for the study, decide to just start taking the medication. Why risk getting randomized to a placebo? All these challenges were met and overcome by perseverance, innovative recruitment strategies and dedicated participants. They should be commended for conducting such a challenging study.

So, today you have the opportunity to do something to empower patients and clinicians to help control this epidemic. You have the ability to empower people, especially women, to take control of their sexual health, and you have the ability to approve a medication that is both safe and effective for the prevention of transmission of herpes infections. All the decisions in your life should be this clear!

DR. GULICK: Thank you, Dr. Davis. Nest is Dr. Hunter Handsfield from the University of

Washington.

DR. HANDSFIELD: Thank you. I put my name in as a place holder in case there were issues that came up that I thought were particularly important that didn't arise, and that hasn't happened.

In the interest of disclosure, I will say that as a public health official responsible for a large HSV control program, I support the application on both clinical and public health grounds, and I think it is also fair to point out that Dr. Haverkos and others at the agency were aware of that support when they invited me to speak this morning. Thank you.

DR. GULICK: Thank you, Dr. Handsfield. The fourth person to sign up is Mark Wasserman, who is the co-leader of HELP of Washington. He is unable to be here today but has a written statement that was made available to members of the committee and it is at the registration table as well. It is not very long, perhaps I will just read through it briefly:

Subject: Submission for FDA hearing on Valtrex supplemental new drug application. This letter for consideration by the FDA advisory committee is to support the GSK application for

Valtrex suppressive therapy to reduce the risk of transmission of genital herpes.

For the past 20 years, I have been a member and leader of the Washington area herpes support group, HELP of Washington. In that capacity, I have heard the personal stories of thousands of people with herpes who have participated in our meetings.

It may be difficult for someone without herpes to grasp the shock, anger, depression, fear and loneliness that a person with the virus may well experience. One of the most often stated sources of this emotional anguish is the fear of spreading the disease to a sexual partner during the most intimate act of human nature. Even after people with herpes have overcome the initial emotional distress that accompanies a diagnosis of herpes, many continue to have difficulty carrying on a normal social life because of this fear of transmission.

Fortunately, the new research showing that daily use of Valtrex significantly reduces the risk of transmission has given hope and encouragement to our members. For many, this information has helped them better deal with emotional problems of living,

dating, telling and loving with herpes. For many uninfected partners of our members, the new has meant that they too can more easily accept having intimate relations with someone with herpes.

It is important that the results of this research reach a much wider audience of people with herpes and their medical practitioners. FDA approval of the supplemental new drug application would help achieve that goal.

Finally, from a public health medical perspective, it is important to curtail the spread of herpes. The new research shows that Valtrex helps achieve that goal. Both in the interest of reducing the spread of this disease and reducing the debilitating emotional distress that often accompanies the disease, HELP of Washington strongly urges the cm to approve the supplemental new drug application for Valtrex. It is signed Mark Wasserman.

Our last person to sign up to speak at the open public hearing is Curtis Phinney, also from HELP of Washington. I hope that you weren't planning to read the letter that I just read.

MR. PHINNEY: No, Mark had the easy part. My name is Curtis Phinney and I am a consumer

advocate for people with viral STIs other than AIDS and HIV, loosely under the auspices of HELP of Washington, DC.

I am currently speaking on an ad hoc basis at the Johns Hopkins University, Bloomberg School of Public Health in a nursing preceptorship program there, administered under the auspices of Keith Aimmerman and Dr. Ann Rampalo.

When I speak to people outside of the consumer group I always like to say that I have five things that are important about genital herpes. That is, genital herpes is chronic, contagious, preventable, treatable, and I think perhaps most importantly very serious. I think that there are two things that are relevant to the committee here this afternoon that may not be intuitive to people outside of the consumer population, and one of those has been touched on already, and that is one of the primary concerns of newly diagnosed consumers, people who join the club, if you will, is the risk of transmission to an uninfected partner. This causes a tremendous amount of psychosocial morbidity associated with the condition, not only the possibility of infecting a current partner, but also adding to the

complexity of attracting and retaining new partners.

The other thing that I think has been touched on earlier is that there has been very little available, other than counseling, in terms of direct chemotherapy intervention for people with herpes that will aid in the dynamics of disclosure. People are not open and honest about having this condition. I came to the realization a decade ago that dishonesty and denial were important factors in the transmission of this condition. That is one of the reasons that I chose to break my anonymity with regard to my serostatus. It is my opinion that being able to offer people with this condition a tool that will prevent or reduce the possibility of transmission to an uninfected partner could have a profound positive influence on the dynamics of disclosure and help not only to dispel the stigma but to also give people a toe-hold in initiating an extremely difficult conversation, laying themselves vulnerable to somebody that they are nervous in the presence of anyway, and being able to say that this treatment will reduce the possibility of getting involved with me having a negative influence on your health.

Finally, I would just like to close, I have a short paper out in the lobby on the impact of prophylactic treatments for people with HSV and HPV, and also contact information is included in that package as well. That is really all I have this afternoon. Thanks very much.

DR. GULICK: Thank you. That concludes the people that signed up to speak at the open public hearing. Is there anyone else who did not sign up who would like to make a statement at this time?

[No response]

Then we will close the open public part of this meeting, which brings us to lunch. It is 12:20. We will reconvene at 1:15.

[Whereupon, at 12:20 p.m., the proceedings were recessed for lunch to reconvene at 1:15 p.m.]

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A F T E R N O O N P R O C E E D I N G S

DR. GULICK: We will reconvene. Welcome back from lunch. Just a reminder both for the committee and people observing, there are the surveys about conflict of interest, if you could complete them and either mail them back in, or there is a box at the registration desk, that would be appreciated.

We left one unanswered question at the end of lunch, which was posed by Dr. Potter about the compliance on the study. So, if we could take a look at those data.

DR. COCCHETTO: Sure. Dr. Potter, I asked Dr. Roger Liddle to look at that and we want to focus initially on the information that we have on source partner compliance among the primary endpoints and also the overall acquisitions.

DR. LIDDLE: Could you bring up slide E23?

[Slide]

This just shows us the compliance rates for the primary endpoints, for the primary infection transmissions. Obviously, more interest is on the Valtrex side. Three of the four transmissions on active treatment were in the greater than or equal to 95 percent compliance.

There was one that was lower but it was in the 80, 85 percent range. The other slide that might be of interest would be E37.

[Slide]

If you are looking at overall acquisition, the same sort of information for all acquisitions, again, there was one patient where I think we actually had some missing data. If the treatment stop date is missing, then we sort of don't have the denominator to calculate the compliance figure. So, I think the one that shows up there is less than 80, a case where we had missing treatment stop date, but overall the compliance was pretty good among the endpoints so there is no strong signal there.

DR. POTTER: What about overall?

DR. LIDDLE: Overall? Let's pull up S5.

[Slide]

It is a little harder to look at this slide but I think here, if you look under placebo down to greater than or equal to 80 percent compliance, you will see 91 percent. The same figure for Valtrex is 93 percent. The only thing sort of disturbing I guess about this slide is there are 40, 41 patients listed under zero with

the asterisk. What happened here is there were patients for whom we had no stop date and, therefore, it is really missing so that zero really includes these patients for whom we didn't have a good compliance figure because we didn't know on what date the treatment was stopped.

DR. GULICK: This information is based on pill counts? Is that correct?

DR. LIDDLE: Yes, that is correct.

DR. GULICK: Great, thank you. We will turn now to Dr. Birnkrant for the charge to the committee.

Charge to the Committee/Questions for Discussion

DR. BIRNKRANT: Well, this afternoon we are looking for a discussion by the committee on the interpretation of the results presented this morning. We are particularly interested in the relevance of the endpoint and the impact of the dropout rate on the trial results.

In addition, we are very interested in the applicability of the data to other populations. We are looking for comments with regard to screening as well.

Lastly, we are looking for the committee's interpretation of the data and the impact on public

health with regard to condom use and abstinence during outbreaks. So, I think we can turn to the first question at this point.

DR. GULICK: So, the first question for the committee to consider is does the information presented by the applicant support the use of valacyclovir to reduce the risk of transmission of genital herpes among monogamous heterosexual couples? Let's have some discussion about the information that we saw today in terms of safety and efficacy, and some other issues that people might want to raise. We will start with Dr. Pazin.

DR. PAZIN: I am very impressed by the data that was presented this morning and that we had previously been given. I think it is a very, very well done study. There are a couple of comments I would like to make. For instance, Dr. Smith sort of alluded strongly to the people that are dropouts and I think for anyone who has ever done one of these studies with genital herpes a 20 percent dropout from 1,400 couples is actually a pretty small dropout. I am not troubled by that at all.

I am a little bothered by the data about Australia and Canada. It was so swayed towards the

efficacy of valacyclovir that you can't help but wonder what if that group had not been included, would the numbers still be statistically significant? They wouldn't be as significant as they are, clearly.

The second comment I want to make is that I have always been impressed by the scientific validity of many of these studies sponsored by industry basically, and I think this is another good example. It is a very, very well done study and I think perhaps the collaboration with the FDA helped that along. I am not as equally impressed by the marketing people from companies and I think I would caution them that everything I got said that it reduces transmission and I think that that is pretty well borne out. I think they like to use the words prevents transmission and I think that is a term that often conveys 100 percent or effective in preventing transmission. When you say effective, it sounds like it is 100 percent. I would say that the committee ought to caution the company to say that it is partially effective or partially preventive or, as they have said in the materials we have gotten, that it reduces transmission.

The third comment I would like to comment on is something I just found out yesterday. I happen to stop by our pharmacy and I inquired as to the cost of acyclovir and the cost of valacyclovir. It turns out, in our hospital, acyclovir 200 mg is five cents; 800 mg is 20 cents. That is the daily cost. But 450 mg of valacyclovir is $17.25, 86 times as much. I think the optimism that I heard about the utility of this, if you really get down to it, an ordinary poor person is not going to be able to afford this drug and I think that we should somehow--if they are going to have this indication, we should somehow try to suggest that perhaps the cost is a consideration. I deal with patients. Formerly I was primarily a research doctor but now I deal with patients and cost is a very, very important thing. So, I just wanted to make those comments regarding the studies.

DR. GULICK: Thanks. Other comments? Dr. Sherman?

DR. SHERMAN: I am curious if the sponsor has any sort of cost-benefit analysis information. During lunch I was kind of jotting down numbers and calculations on the back of a piece of paper, looking at the number needed to treat for effect.

Obviously, with a transmission rate that is in the two to three percent range, reduced to a half percent range, you have to treat for extended periods of time many patients to get that benefit. You know, I freely admit that there is a large number of patients infected but when I looked also at the numbers related to cost of the product as listed, current retail cost, you know, again just back of pad calculations came out to some place between $110,000 and $120,000 per case prevented, which goes beyond the typical accepted numbers that people use in prevention programs--in evaluation of vaccines, in other interventional procedures.

So, I am not questioning the data related to the efficacy of the treatment. I think that the sponsor did a great study on a difficult population and has presented and satisfied my concerns about efficacy and safety. But I think that at some place in this equation has to be the answer to the question that I am posing.

DR. GULICK: Would the sponsor like to respond? Is there any cost-benefit analysis data?

DR. COCCHETTO: A couple of comments. Part of the response lies in the patient population that was selected for the trial, as I am sure you

recognize. We selected a patient population who were candidates for suppressive therapy. Let me ask Dr. Young to comment further from a cost-benefit perspective and your comments on numbers needed to treat.

DR. YOUNG: Just to pick up on Dr. Cocchetto's comment, I mean, the way that we have actually approached this is to think of it in terms of an incremental benefit for prevention of transmission, in addition to the benefit that is already afforded to the person who is actually receiving suppressive therapy. So, when we think about the number needed to treat in that circumstance, it is probably on the order of one or less than one. Certainly what you do see is a reduction in the frequency of recurrences, again, among those individuals who would be receiving suppressive therapy.

We have thought about the number needed to treat in order to prevent a transmission event, and what we have come up with is an annualized event rate of about 40 in terms of the number needed to treat but, again, the way we have thought about this really has to do with thinking about what the incremental benefit is for someone who is already

benefiting from suppressive therapy.

DR. GULICK: Dr. Englund?

DR. ENGLUND: Well, I would just like to make a comment related to that, particularly from the pediatric viewpoint, and that is that one case of neonatal herpes--there are different estimates as to cost and I am not the expert on this, but a cost estimate of $500,000 to a million per case survivor is certainly typical, and that is because the children survive. Fifty percent have prolonged, permanent neurologic sequelae. There is no institutionalization currently available. They are requiring special ed. The state is required to send them to school, which costs a lot of money, even though many of them have very limited potential for learning. So, the cost for the children would be really high and if any cost-benefit analysis were to be made, I would strongly urge that the consideration of the children be considered. Particularly in this small study for a small period of time, it appeared to me there were 18 pregnancies during an eight-month study period. That is a lot of potential babies. So, the potential benefit to prevention of transmission to women of childbearing age really

needs to be considered when anyone is considering doing this. I believe the cost and other things need to be considered, but I don't want to forget the children out of this analysis, which is certainly not the primary endpoint of the study but will be a consideration for people in my clinic and other clinics when there are couples that want to have children.

DR. GULICK: Other general comments and then I am going to try to focus us a little bit? Dr. Fish?

DR. FISH: I think adding to that the information that we learned this morning in terms of the potential increased greater transmission of HIV, if one HIV case is not transmitted there would also be a huge impact there.

DR. GULICK: Dr. Guinan?

DR. GUINAN: I would just like to add that for HIV patients with herpes simplex infection this is an important consideration because probably their recurrences are much greater and their asymptomatic shedding is probably more frequent, although there is limited data. The possibility that an HIV-positive person will transmit HSV to a partner who may be negative, you know, discordant

partners for both, and I have seen this in heterosexual couples with a much younger female partner and the worry is about transmission of HSV and HIV. I think this subpopulation, although may be small--it is very important because if the partner gets HSV infection then they are at higher risk for getting HIV infection. You see? So, the primary prevention of HSV acquisition in this discordant relationship is very important. So, there are subpopulations where the cost effectiveness or cost-benefit analysis would be, I think, quite different depending on what the values and assumptions are.

DR. GULICK: Can I ask Dr. Handsfield or Dr. Corey about information on HIV-infected patients in terms of numbers of recurrence of HSV and amount of viral shedding, just to clarify that point?

DR. COREY: Well, it is very variable. Certainly CD4 count and viral load are factors and, as you would expect, the lower the CD4 count, the higher the viral load, the more shedding. I think the most surprising thing, however, that has occurred and in the paper that has been submitted from our group, is that while therapy decreases the

frequency of genital lesions does not decrease the frequency of total inactivation and subclinical reactivation. So, it is and continues to be a problem both in the treated and untreated populations.

DR. GULICK: Thank you. Dr. DeGruttola?

DR. DEGRUTTOLA: I would just like to say in response to this question that I think that the information presented did support use of valacyclovir to reduce risk of transmission of genital herpes, but the results are still not quite as reliable as one would hope because of lingering issues about the high withdrawal rate. Even though I think the study was done under very difficult conditions and that withdrawal rate may be all that can be hoped for, there are still some concerns there as with the geographic variation. Despite those concerns, I would still answer in the affirmative.

But given that we did see strong evidence for the effect of valacyclovir on viral shedding, on number of episodes and so on--and this may come later, but some further research to try to understand transmission better might help increase the degree of certainty that the question truly has

been answered in the affirmative.

DR. GULICK: Let me just remind the committee, we will take a formal vote on this question at the end of this discussion. Don't feel like you need to say what your vote is going to be at this point because each person will get the chance to vote, but comments are welcome.

Let me try to focus us a little bit. Safety, let's consider safety for a minute. We have heard some sort of general comments. Are there more specific comments to make about safety in terms of what we saw? Dr. Guinan?

DR. GUINAN: I would say that it is an impressive record of safety. The adverse reactions are headaches for the most part. Clinically that is what I see. What we don't know is long-term but, even so--you know, what if you treat someone for 20 years for example--those data are not available. My suggestion on that would only be that there needs to be postmarketing surveillance somehow developed for long-term use of acyclovir and valacyclovir for trying to understand that. In other words, does 20 years of therapy mean that there is a larger risk, or are there just these rather minor effects that we see, adverse effects

of therapy?

DR. GULICK: Let me remind the committee that that is a whole separate question that we are going to answer about the longer-term side effects. Yes, Dr. Kumar?

DR. KUMAR: When acyclovir is used in high doses I know it crystallizes and causes stones in the kidney, and please correct me if I am wrong. So, I was a little intrigued by the one patient that had hematuria that the sponsor said may have a stone. Do we have any further information on that patient? There was one patient with hematuria.

DR. COCCHETTO: We don't have further information on that patient. Dr. Haverkos mentioned it in his case presentation and he may wish to comment.

DR. HAVERKOS: Well, I have the narratives and I actually went back to try to find that narrative again last night and I couldn't find it, but it is one that we need to look at again.

DR. GULICK: Further comments about safety? If not, let's turn to efficacy. We already considered this somewhat. Are there additional comments about efficacy? Dr. Washburn?

DR. WASHBURN: I have a question for Dr.

Smith. I too am fascinated by this geographic breakdown. To put it bluntly, I wonder if the differences in the observations in Australia versus eastern Europe are likely to be by chance alone.

DR. SMITH: I didn't do a formal comparison with just Australia compared to eastern Europe but the overall comparison between all of these, I think six different regions, is statistically significant. You know, a p value of 0.01 is quite a bit less than 0.05 although they do have multiple comparison issues. You know, that is a good question. I don't know.

DR. GULICK: Other comments about efficacy? Could you introduce yourself to the committee?

DR. SOON: My name is Greg Soon, FDA. Regarding your question about interactions that you were asking, is the effect size different between different regions--I assume that is your question. If that is your question, then the answer is that the p value for that was fairly large. I don't remember the exact numbers but it is somewhere about 0.3 or 0.5 so it is pretty large. So, really we do not have evidence to say the true differences are different between regions, but we do have

evidence to say that the response rates are different among different regions.

DR. WASHBURN: Speaking naively, it just looked like the drug worked in Australia and it didn't work in eastern Europe. What I am hearing is that probably wasn't statistically significant, that I should ignore that, that that is background noise. I can think of it as a Poisson distribution; it could have been the other way around. Is that right?

DR. SMITH: Yes, that is probably correct in terms of the treatment differences. In terms of the evaluation though, you know, there could be some kind of response categorization bias or response category bias where they have different ways of ascertaining the endpoint in eastern Europe and western Europe than then do in Australia and the United States.

DR. GULICK: Dr. DeGruttola, would you agree?

DR. DEGRUTTOLA: Well, I can just comment on what the FDA statisticians are saying and actually just reviewing the data, because of the small numbers, it doesn't surprise me that they don't find an interaction of the treatment effect

itself with geographic region, but do find that geographic region affects the endpoint rate. So, the analysis that the FDA has reported on seems to me to jive with what I would expect from looking at the numbers.

DR. GULICK: Dr. Fletcher?

DR. FLETCHER: My question is for the sponsor on the efficacy issue, and I am wondering whether you have any information, and I realize how small the sample size is, but it is to the issue of correlates with efficacy or with the prevention of transmission. What I am particularly thinking is in terms of trying to provide information to a physician, to patients--again if there is a recommendation for approval--that would use this. It would seem to me one dose, for example, is not likely to be effective so there is probably some duration of time on therapy before there is efficacy and I am wondering if you have any information on that issue.

DR. COCCHETTO: I think we can help to some extent with that. Let me ask Dr. Wald to comment.

DR. WALD: Anna Wald, from University of Washington. In our shedding studies it appears

that the amount of virus present after initiation of antiviral therapy decreases in about three to four days, and then achieves sort of a complete low baseline in five days. The same is also true when you discontinue therapy. There is a slow rise over three to four days and then it goes back to baseline levels at five days.

DR. GULICK: Additional points about efficacy to raise? Mr. Ebel?

MR. EBEL: I wanted to comment from a patient point of view on the efficacy question and to put it in kind of a real-world frame of, you know, compared to what. Obviously, we have heard already some pretty compelling statements from people to the extent that wanting to protect a sexual partner is a major concern for people who have genital herpes and the risk reduction measures they have at their disposal now are very limited. While condoms are recommended and may be a good option for a lot of people, I think probably we would all agree there is pretty limited data on that.

So, I guess from a patient point of view, it seems to me that this range of efficacy data we are looking at, whether it is 75 percent or the 50

percent seroconversion protection, would be regarded by people with herpes as a huge gain compared to what there is.

DR. GULICK: Thanks. Dr. Mathews?

DR. MATHEWS: Two points. I already mentioned the issue about potential misclassification in terms of the dropout rates. I would suggest that the agency request the analyses on frequency of sexual intercourse and condom use at least at the baseline time point to be sure that there was no differential effect in dropouts.

The other thing with regard to efficacy is that while the point estimate of 75 percent risk reduction is clearly significant and consistent across even the secondary endpoints, the confidence limits on that point estimate are very broad. They go from 0.08 to 0.75. So, when you go to craft an efficacy statement in terms of what the prevention message is and how effective this is, somehow the uncertainty in that estimate has to be conveyed.

DR. GULICK: Dr. Birnkrant?

DR. BIRNKRANT: Building on Dr. Mathews' statement, we would also like the committee to discuss the relevance of the other endpoints, namely the overall acquisition, because this will

be important to us with regard to labeling of the product. So, if we could get a discussion on the importance of including that type of data in labeling in addition to the primary endpoint, which is the main focus. We would also like to have input on the other endpoints as well.

DR. GULICK: Just to remind us all, the primary endpoint was clinical episodes of HSV-2, and then seroconversion was a secondary endpoint. Overall acquisition would sum those two together. So, what do we think of the choice of the primary endpoint and the other two endpoints? Dr. Englund?

DR. ENGLUND: I personally think that the serologic or total endpoint is actually much more important. If I were to be asked about future trials, that is what I am interested in. I am saying that for several reasons. I think we know more now than we did perhaps back then about the asymptomatic shedding and the high prevalence of asymptomatic shedding. I, as a pediatrician, see babies born, like last week, where the mothers didn't know they had it because it was asymptomatic shedding. That is, in fact, very, very common. So from my viewpoint, I would be interested in the total. And serology, I was trying to get at that

in my earlier question, I think serology is a very good reflection.

Furthermore, for future studies by relying on serology it might make it easier to do a study. This study is heroic. This is absolutely heroic to have people doing as many cultures as they are doing. I think if it were a simpler study design perhaps, maybe not, you could get more people involved. But disease as measured by serology, for me, is important because I think it would really help couples know what is going on and it certainly would help in terms of the babies born.

DR. GULICK: Other comments on endpoints? Dr. Guinan?

DR. GUINAN: Yes, I agree with Dr. Englund. I think that there is a great deal of asymptomatic infection, not only asymptomatic shedding but asymptomatic transmission in which the partner does not have any clinical symptoms or signs. So, this is a very important aspect of the epidemiology. It is not terribly important from a clinical point of view of treating people because they don't know they have it so it is sort of our of the clinician's purview. But I think if we looked at it epidemiologically and were interested

in prevention or reducing transmission, that is a more logical and more accurate endpoint about reducing transmission.

DR. GULICK: Dr. Fish?

DR. FISH: Yes, I think I would agree with those comments. When I was first reading through the briefing document that was the question that came into my mind, why wouldn't we want to know about overall acquisition and knowing that there is the risk for shedding and increased risk for potential transmission? It does, however, diminish the apparent treatment effect when you look at a study that only would have serology-based data based on the data that was presented here today.

DR. GULICK: The last special issue to consider with the question from Dr. Birnkrant is the dropout rate. We have talked a little bit about this already. Are there additional comments to make about the dropout rate versus the endpoint rate? Dr. Washburn?

DR. WASHBURN: Just a quickie, I would assume that they would be equally distributed through the two arms of the study so they didn't bother me.

DR. GULICK: Well, let me try to sum up

what we have said. Consensus of the committee is that we found the efficacy and safety data impressive and the study well done. We found that the drug reduces transmission but would caution not to use the word prevent. It also has some side benefits about reducing HIV transmission and reducing shedding; the repercussions of the social aspects of this in terms of reducing anxiety among infected people in terms of transmitting to their partners.

We did have some cautions. One was Dr. Mathews' point about the wide confidence interval around the point estimate that we saw in terms of the data. The choice of endpoints generated some recent discussion. People felt that perhaps a serologic endpoint or overall capturing both clinical and serological endpoints was actually preferred or would be preferred in future studies. This may be more logical, in the words of Dr. Guinan. We certainly appreciate more asymptomatic shedding and transmission and this could be an easier endpoint to assess. That was Dr. Englund's comment on future studies.

Other concerns that came up in our discussion are the low number of endpoints compared

to the number of patients treated. We spoke of the high dropout rates that were observed, although some people were less concerned than others in terms of the overall effects on the primary endpoint. Dr. Mathews cautioned us about differential effects among the dropout populations.

There are lingering concerns about geographic differences and why those occurred and how to explain that; some concerns about the demographics of the population studied. We mentioned earlier today--Dr. Kumar brought out the point that 90 percent of the population studied were white and I think the committee felt that we would liked to have seen more information in other groups as well. We heard some caution about the duration of therapy. We are going to have another opportunity to discuss that in terms of long-term safety.

Then, another issue that we don't often discuss as a committee is cost of medication but that was raised early, and the cost-benefit analysis and how does this compare with other interventions that we use, although several cautions about what is the relative cost of preventing an HIV infection or preventing

complications, for instance, in the pediatric group. So, that remains an open question but one that generated some interest among the committee.

With that, we are going to take a formal vote and read the question one more time: Does the information presented by the applicant support the use of valacyclovir to reduce the risk of transmission of genital herpes among monogamous heterosexual couples? So, a vote "yes" would be for approval and a vote "no" would be against approval. Mr. Ebel and Dr. Stone, you are not eligible to vote so I am going to go around the table and ask people to vote yes or no, and start with you, Dr. Potter.

DR. POTTER: Yes.

DR. GULICK: Dr. Guinan? Turn your mike on.

DR. GUINAN: Yes.

DR. GULICK: Dr. Pazin?

DR. PAZIN: Yes.

DR. GULICK: Dr. Fish?

DR. FISH: Yes.

DR. GULICK: Dr. Washburn?

DR. WASHBURN: Yes.

DR. GULICK: Dr. Mathews?

DR. MATHEWS: Yes.
DR. GULICK: Dr. Fletcher?
DR. FLETCHER: Yes.
DR. GULICK: Dr. Stanley?
DR. STANLEY: Yes.
DR. GULICK: She is hanging in there! Dr. Kumar?
DR. KUMAR: Yes.
DR. GULICK: Dr. Sherman?
DR. SHERMAN: Yes.
DR. GULICK: Dr. Englund?
DR. ENGLUND: Yes.
DR. GULICK: And Dr. DeGruttola?
DR. DEGRUTTOLA: Yes.
DR. GULICK: And the chair votes yes. That is unanimous, 13 votes for "yes" and no votes for "no." Let's take a five-minute break.
[Brief recess]
DR. BIRNKRANT: That was the easy part of the afternoon.
DR. GULICK: I know. Thanks for reminding us. Now the working part comes into play. Let's go to question number two: Does the information presented by the applicant support the use of valacyclovir to reduce the risk of transmission of

genital herpes among populations other than monogamous heterosexual couples? Dr. Mathews?

DR. MATHEWS: Well, to get it started, the first thing I would say is that I don't see any reason to restrict it to monogamous heterosexual couples. I think, at least to my mind, there is no biological reason why that should have anything to do with the efficacy of the intervention.

However, I don't think it should be an indication for immunocompromised heterosexual couples, whether by HIV or anything else, since that was an exclusion. Although it is likely to have some efficacy, we don't know anything about whether this would be the appropriate dose, for example, in immunocompromised populations.

I also don't think that it should be generalized to non-heterosexual couples for similar reasons. We just don't know whether the intervention would have a comparable efficacy, and also the prevalence of HIV in men who have sex with men would likely attenuate the effect. So, those are my opinions.

DR. GULICK: Other thoughts? Dr. Potter?

DR. POTTER: Just a very brief one, the more different kinds of methods you are using to

prevent transmission, the better. In other words, this and condoms, although condoms are not used very much, literally because of compliance issues, the more the better.

DR. GULICK: Dr. Guinan?

DR. GUINAN: I don't really know very much about the quantitative aspects of HSV. I am just not familiar with the methodology. But it is clear that if valacyclovir reduces the quantity of virus shed, and in all infectious diseases we presume that there is a minimal infective dose for infection and it may vary with host factors so, from a theoretical point of view, in whatever population you use this there would be a decrease in quantity of virus and rate of shedding. So, I believe that that could be extrapolated to all populations. In other words, that the effectiveness, based on sexual orientation or whether you are monogamous or not, shouldn't be different.

As far as whether the social circumstances are different, that is a question that I think we can't answer, but from an effectiveness point of view, I don't think you can argue that it is unlikely to decrease the quantity of virus in

somebody who is not monogamous or who is not heterosexual.

DR. GULICK: Dr. Mathews, a response?

DR. MATHEWS: Well, I would agree that it is likely to have some effect but how could we estimate the magnitude of that effect? Is it 0.75 in an immunocompromised patient or a gay male who is predominantly having anal receptive intercourse? I mean, on what basis would you estimate how protective it would be?

DR. GUINAN: Well, I certainly wouldn't estimate that but I would just say that from a logic point of view it would reduce it. Whether it would reduce it sufficiently to be protective at the same rates as it is in this study I don't know. But it would seem logical that it reduces the rate and magnitude of virus and the shedding. I think that is extrapolatable to gay--I am not talking about immunocompromised but I would say a non-heterosexual, non-immunocompromised individual. I can't see any reason why this wouldn't be translatable.

DR. GULICK: So, as a committee we have faced difficult questions like this before. We have seen data in one population and we have

biologic plausibility, but we have no data in other populations and how do we translate that into what goes into the label? How do others feel about that? Dr. Sherman?

DR. SHERMAN: I think that, as has perhaps already been said, we can translate this into heterosexual immunocompetent couples but not beyond that. The monogamous was a mechanism to do the study appropriately so that certainly should not be an issue in the equation. Everything else follows right after that in terms of people who are immunocompetent and have heterosexual contact.

DR. GULICK: Dr. Kumar?

DR. KUMAR: From everything that I have looked at in the data, I think this data is applicable only to heterosexual immunocompetent couples. I think to make the leap of faith, even though biologically it may make sense, especially with the issues we spoke earlier about, it is efficacious but not the effective method of decreasing transmission. I would be very uncomfortable to make that leap of faith to anything other than immunocompetent heterosexual couples, especially when it comes to immunocompromised HIV patients.

DR. GULICK: Dr. Pazin?

DR. PAZIN: I would just agree with that. I think immunocompetent heterosexual is probably as far as you can go on this study data.

DR. GULICK: Any other thoughts on this or disagreement?

DR. GUINAN: Yes, I disagree that you couldn't in an immunocompetent non-heterosexual--I don't see that the data on shedding of virus and of reduction in quantity of virus--there is no biologic known difference between non-heterosexuals and heterosexuals in handling infections if they are immunocompetent. So, I would disagree that this should be limited to immunocompetent heterosexual. I think that immunocompetent non-heterosexuals would also--it would apply also. I can't find a logical reason why it wouldn't.

DR. GULICK: Dr. Sherman?

DR. SHERMAN: I wonder if any of the expert members on the sponsor's team have an answer to this, but I suspect that immunosuppressed patients have higher titers and for a given level of reduction there is probably some threshold level that you see a significant reduction in risk of transmission below that point. If that is the

case, and it is the case with many other viruses, if we see an average, just to throw out a number, of a half log decline in virus and you start two logs higher you may have absolutely no apparent effect in transmission for this particular virus. I think that that would really need to be tested.

DR. GULICK: Dr. Birnkrant?

DR. BIRNKRANT: Could we also get comments on use in adolescents and how do we deal with the susceptible partner not being monogamous?

DR. GULICK: Let's take adolescents first. Dr. Englund?

DR. ENGLUND: Well, adolescents don't use condoms. We try and try and try and they don't use condoms even when they are HIV-infected and they know it. They don't tell their partners frequently and they don't use condoms. I think this HSV approach might be another way to try and get them up to speed to acknowledge that there is a problem. There is certainly double seropositivity in these and I think for my patients and my clinic that this will be a good approach. Not that we are ever going to tell them to stop using condoms; we don't want them pregnant, but they are getting pregnant every day too. So, they obviously aren't using

condoms even when they tell us they are using condoms, which they do tell us but they aren't.

So, I think that this is an important adjunct. I think that people of childbearing age range are where this drug could be focused from a public health point of view because of the multiple sequelae--HIV, the childbearing. And, I see no problem with having this part of an adolescent clinic. We start usually around 11 or 12 years for this kind of thing. We don't know long-term effects. I would encourage that we need to have long-term efficacy and safety but I think it fits right in with what we are doing and gives us yet another reason to talk with them every month, which is what we are doing.

DR. GULICK: Other comments about adolescents? The other population was?

DR. BIRNKRANT: When the susceptible partner is not monogamous. Is that an issue for any of the members on the committee?

DR. GULICK: Given our previous discussion about monogamous couples, I am guessing not.

DR. BIRNKRANT: Okay. And what about Dr. Stone, being from the CDC, do you have any additional comments on this question?

DR. STONE: I think I agree that immunocompetent heterosexual populations could be included. I have some reservations about men who have sex with men. I would have no problem including adolescents.

DR. GULICK: Dr. Pazin?

DR. PAZIN: This thought that a susceptible partner--it is irrelevant. Obviously, it is not going to provide protection for other people who aren't using the medication. So, that just goes without saying as far as I can see.

DR. GULICK: So, let me summarize what we said about populations. First of all, a reminder to us that education about herpes and transmission and the overall thought that there are other methods of avoiding transmission, including condoms, continues to be important. What is recognized here is biological plausibility of an antiviral agent to reduce the amount of virus. Then, some differences of opinion about how much one can extrapolate to other populations because of differences in the amount of virus and how much it may or may not go down; the differences in effect from population to population and the magnitude of response.

As Dr. Sherman pointed out, monogamous was really a requirement for this particular trial and allowed the study to be done but, as many have echoed, it is not an important criterion for achieving benefits in immunocompetent heterosexual couples. That is the best data we have that we have seen today.

There was more concern in homosexual couples, although not uniform opinion on whether one can extrapolate data from heterosexual to homosexual couples, and simply no data to guide us at all.

There was endorsement among adolescents for the same reason that adults would benefit, and perhaps even more of an endorsement in adolescents given problems with condom use and opportunities to discuss reduction and transmission. Because adolescents are younger, longer-term data is going to be even more important in this group perhaps.

Then, a consensus that it is probably not appropriate to extrapolate to the immunocompromised host because of concerns that viral burden may be higher in this population and that, again, we simply don't have the data to make those recommendations.

We suggested some longer-term studies in the course of our conversation here. Dr. Sherman earlier said that transmission studies would be of interest, and perhaps relating the amount of HSV or the HSV titer to transmission is something that we could know about more.

I guess we would like to see studies in immunocompromised groups. We would like to see studies in gay men and women. Again, the longer-term safety issues were something that is of paramount importance. Dr. Mathews?

DR. MATHEWS: One implication I think of what we have recommended is that the label should I think somewhere contain a recommendation that people be encouraged to have HIV testing before this decision is made to prescribe this. I mean, the same population should have been HIV tested anyway, I would think, especially if they are not monogamous. We should find a way to put that in there.

DR. GULICK: Just to remind us from the sponsor point of view, in this study everyone received HIV testing and that was an exclusion criterion? Is that correct?

DR. HARDING: There was no HIV testing.

They were excluded if they had a history of HIV. We also went through the case records after the study had completed to look for any indication of HIV and there was none, nor were there any medications used for HIV.

DR. GULICK: So, by history HIV was an exclusion but serologic testing was not performed on the study?

DR. HARDING: Right.

DR. GULICK: Thanks for that correction. Dr. Fletcher?

DR. FLETCHER: On your list I think you would want studies in adolescents as well. I am not saying, you know, a thousand patients. In this study it only went down to 18 years of age and while I don't think that the pharmacokinetics of valacyclovir are going to be different in adolescents, without data--you know, there are always surprises out there. So, I think if you are going to make that extrapolation to adolescents there needs to be some basis to do that. At least from the most simple point of views, a pharmacokinetic study of valacyclovir in adolescents would be one way to understand whether the concentrations at a 500 mg once daily dose are

going to be equivalent to those seen in adults.

DR. GULICK: Does the sponsor have data on PK in adolescents with valacyclovir?

DR. COCCHETTO: I am looking to Dr. Weller here. Steve? Stephen Weller is in our clinical pharmacology group and he can comment.

DR. WELLER: We don't have specific pharmacokinetic data in adolescents per se since studies have been done in younger children, much younger children with acyclovir, historically. Children as young as 12, 13 years of age have been included in some of the Phase III trials for some of the indications but, again, specifically as pharmacokinetic data in adolescents, we don't have that at present.

DR. GULICK: Dr. Pazin?

DR. PAZIN: Yes, I was thinking it would be interesting to get the committee to vote on the concept of whether we think it should be extendable to homosexual couples.

DR. GULICK: Okay, a non-binding kind of straw vote.

DR. PAZIN: Sense of the committee.

DR. GULICK: Let's just do it--

DR. GUINAN: Immunocompetent.

DR. PAZIN: Immunocompetent homosexual partners. Do you think it should be extended to them or not?

DR. GULICK: In other words, extrapolated on the basis of labeling, whether we would recommend that for labeling or not. Dr. Handsfield, did you want to make a comment?

DR. HANDSFIELD: I would just point out that in that discussion what has not been raised by any of you is differences in sexual practices in particular because it is conceivable that at a biological level it is not just viral load, but what is the level of the kind of exposure that takes place, for example, during anal intercourse as opposed to vaginal intercourse and potential microscopic or overt trauma that might affect transmission rates. So, in thinking about that vote I would be inclined to factor that into your thinking.

DR. GULICK: Dr. Guinan?

DR. GUINAN: Well, in the study was it determined what types of sexual intercourse these monogamous couples had? Was it restricted to vaginal-penile intercourse?

DR. GULICK: Unlikely to be restricted--

[Laughter]

DR. GUINAN: What I am saying is that it is very possible that there was rectal intercourse among these couples.

DR. GULICK: Does the sponsor have any information on what kind of intercourse occurred on the study?

DR. HARDING: There was no restriction on anal intercourse. There was some but it was a very small number. We do have the numbers if you require them, but I can't recall them off the top of my head. The median was zero obviously.

DR. KUMAR: I think your page 44, table 8, would that not give us information we are looking for?

DR. LIDDLE: I think it looks like eight percent according to the diary data.

DR. GULICK: Again just to clarify, the way that this was assessed was by patient diary? Is that how it was? So, people were expected to jot down what was going on over the last 24 hours in their diary?

DR. COCCHETTO: That is correct. Susceptible partners maintained a diary that was returned with each monthly clinic.

DR. GULICK: Additional comments about extrapolating to the homosexual immunocompetent population before we take a straw vote? Dr. Mathews?

DR. MATHEWS: I just one to make one last comment about this. I don't think it is a matter of whether it is a good idea or is biologically plausible. It is a matter of is the evidence sufficient that it should go into a label and my opinion is definitely not. It should be studied and there should be the same kind of evidence for the MSM population, for the reasons that have been stated previously as well as what Dr. Handsfield just said.

DR. GULICK: Dr. Corey, do you want to chime in?

DR. COREY: I think everybody is right--

[Laughter]

--but I would say that there has not been a partners study published in the HIV literature, and certainly not in the herpes literature that I am aware of, that has been successful in looking at transmission among gay men solely, monogamous gay. So, the study design, and we have thought about this, we don't think is a possible study design to

get enough monogamous gay men. So, you would have to think of a more unique design or that could be done in a unique population-based basis, or something. But it would certainly be a very unique study design as far as I am aware of in the field of STDs.

DR. GULICK: Just to be clear, did you say that previous studies have been attempted or designed and were unsuccessful in enrolling? Discordant gay couples, those studies have been largely difficult to perform is what you are saying. Other comments? Dr. Fish?

DR. FISH: I think that said, I would agree with Dr. Mathews that I am not sure how we would extrapolate to this patient population. It is a large leap of faith and whether the study can or can't be done, it seems to me like the labeling would better address the information that we have, letting people decide based on the information that is there and the data that is available, people being practitioners.

DR. GULICK: Dr. Guinan?

DR. GUINAN: I would just like to say I have worked for the CDC for a long time and was in charge at one time of developing the STD treatment

guidelines, and all that was done on scientific studies, it was not until very recently that sexual orientation ever entered into the discussion. In other words, you didn't know what the sexual orientation of the patient was. It was whether it was effective or not effective. Do you see what I mean? So, it is very difficult for me to now differentiate those and say, okay, this is good for heterosexuals and to make a recommendation, for example, if CDC were incorporating these into the treatment guidelines, to say, oh, this is good for heterosexuals but we don't recommend it for homosexuals, or there is no data on homosexuals. Do you see what I mean? So, I understand everybody's concerns but to think that there are biological differences in the way people process these drugs because of sexual orientation, to me, is not plausible.

DR. GULICK: Dr. Stone, could you comment on implications for guidelines?

DR. STONE: Let me also just say as regards the applicability of this to gay people, I think our concerns were more specifically for MSM--not all MSM but not just HIV co-infection but just the general sexual practices may be very

different.

This study population did have anal intercourse but it may be with a different frequency than men who have sex with men. But when the time comes for us to, you know, update our treatment guidelines we would--I can't tell you now what we would do but in each section of our guidelines we have a special section on special populations and we specifically comment on HIV-infected persons. To my knowledge, we don't have anything in here about homosexual versus heterosexual patients or partners.

Another approach would be to speak of vaginal intercourse versus anal intercourse and you could get away from the sexual orientation label.

The other thing about this study, if you were really restricting the applicability, then it would be applicable almost to very few people because if you look at the frequency of sex in this group, they really were not very sexually active but I don't think anyone here wants to limit the indication for people who have sex six times a month.

[Laughter]

So, I think it is a fine line between, you

know, generalizing too broadly and being too narrow.

DR. GULICK: Any Australians in the crowd?

[Laughter]

Dr. Englund?

DR. ENGLUND: I just wanted to say that it was actually the women though who drove the study or the vaginal intercourse. That is, before the study the investigators knew that. That is why the study tried to be stratified, ultimately unsuccessfully. When you look at page 56 and the table, it is 7.5 percent of the women in the placebo group and only 1.0 percent of the men. So, it is the women, in fact, that may have benefited the most, which is good news for women, but to be able to translate that into men only and then men having sex with men in addition, that is making two leaps of faith instead of just one. So, even though I think biologically it might be the same, I think the practices vary and I think we, as the advisory group, need to take that into account.

DR. GULICK: Dr. Smith?

DR. SMITH: As I recall, there was no treatment by gender interaction so the treatment effects in men were basically similar to the

treatment effects in women. It is just that both treatment groups had a lot of fewer events. So, I would say that the results probably are generalizable to men among heterosexual monogamous couples.

DR. GULICK: Then, if we take anatomy as the likely explanation for differences in transmission, receptive anal intercourse may be more analogous perhaps to men having an increased risk to transmit to women, although we don't know. Lots of leaps of faith here. Dr. Smith?

DR. SMITH: There is only the median of zero. You know, the number of anal sexual contacts is zero for the overall population. So, it is almost all non-anal sex in the study.

DR. GULICK: So, we have heard a lot of differences of opinion and this is kind of a non-binding vote but might be of interest to the agency if pin people down. So, let's just raise our hands and Mr. Ebel and Dr. Stone, we will invite you to vote in this one too since it is just an opinion thing. So, a vote for "yes" is that we would not recommend restricting the label on the basis of heterosexual versus homosexual. In other words, that would simply not be in the label. Is

that phrased okay?

Let me try this again. You would support the use of valacyclovir to reduce the risk of transmission of genital herpes, period. No caveats about monogamous and no caveats about heterosexual.

DR. PAZIN: Is that the question?

DR. GULICK: I thought it was the question.

DR. PAZIN: I don't think you are stating it very clearly. I want to make a distinction between heterosexual couples and homosexual couples. I think that is what the discussion has been talking about.

DR. GULICK: That is what I was trying to do. I am just taking the question and eliminating the last part. The question to the committee, and this is a straw vote, is does the information support the use of valacyclovir to reduce the risk of transmission in genital herpes, period? Or, if you like, in both homosexual and heterosexual couples. Is that clear? All in favor of including that sentiment in the label, raise your hand.

[Show of hands]

Two votes. All opposed?

[Show of hands]

So, you get the idea. It is a straw vote.

MR. EBEL: Mr. Chairman?

DR. GULICK: Yes?

MR. EBEL: To me, I would just like to reiterate the confusion about calling the question. Are you going to follow-up now with a more exclusive definition of extending it, in other words, dropping the monogamous part but keeping the heterosexual part?

DR. GULICK: Our purpose today is just to provide some discussion about considerations for the label for the FDA and the sponsor to go forward with in further discussion. We don't have to sort of hammer out the terms of the label itself. We have already voted to say that we would recommend approval of the drug. At this point, all of the other questions really speak to the fact about what should go into the label. So, I don't think we have to get into the nitty-gritty of exact wording for the label. It is helpful I think for the agency--correct me if I am wrong--to hear that there are differences of opinion on the committee. We were pretty uniform about not including monogamous and then there was a difference of opinion about stipulating heterosexual versus not.

But I think we can probably leave it at that and keep going.

MR. EBEL: I was just concerned that the monogamous piece was getting lumped in with the sexual orientation piece.

DR. GULICK: No, I think we have separated those two issues.

MR. EBEL: Thank you.

DR. GULICK: Let's go on to the next question. In study 3009 over 4,000 couples were screened but only about 1,500 were enrolled. A large number of couples were excluded because susceptible partners were found to be HSV-2 positive without clinical symptoms. Please discuss the implications of screening susceptible partners for HSV prior to initiating therapy of the source partner with valacyclovir. Again, this is thinking about the label. Dr. Mathews?

DR MATHEWS: Well, here the scenario changes quite a bit when you broaden the indication to non-monogamous couples because really the treatment in that setting is not a matter of a discussion between a source and a specific susceptible. It really is almost assuming that the source might have sexual contact with more than one

or many people, in which case the education I think becomes very important for the clinician prescribing or contemplating prescribing the drug to talk with the patient about, you know, are you sexually active now, or are you going to be, are you going to discuss your serostatus with your partners. The question is, if they are casual partners, it is not really feasible to recommend, oh you know, you should go out and get tested before you have sex, if you are going to have sex on a casual basis.

I am just thinking now. In the context of an established relationship it might be reasonable to recommend testing the partner. But if it is not a monogamous relationship I wouldn't necessarily put that in.

DR. GULICK: Other thoughts on this? Dr. Kumar?

DR. KUMAR: I am looking at this a little bit differently. If the susceptible partner is positive, then there is no reason for the source person to take the drug. Why would they have to take it for a prolonged period of time if the benefit is not going to be there?

DR. MATHEWS: But they might have another

indication for taking it to suppress their own reactivations, which is already an approved indication.

DR. KUMAR: That is different but right now we are looking really for this indication of preventing transmission. In that, if the susceptible person is already positive, then there is no reason for the source person to take the drug. So, I would recommend that the susceptible partner needs to be tested.

DR. GULICK: Would you require it or consider it?

DR. KUMAR: I would strongly consider it. This is not a drug that you are going to take for a week, two weeks or three weeks. As long as that person is in that relationship you are going to take it every day.

DR. GULICK: Dr. Englund?

DR. ENGLUND: I think we should strongly recommend it for this indication because there is a great deal of money involved; there is potential safety and toxicity and if they are taking it you should know that it is for a reason. A serologic test costs under $50 which is, whatever--three weeks of pills. It really makes sense medically,

socially and economically.

DR. GULICK: Dr. Pazin?

DR. PAZIN: I fully agree that we should strongly recommend getting tested.

DR. MATHEWS: But how would that work in the casual partner setting or adolescents? What does that mean?

DR. PAZIN: To be using the drug as a prophylactic if it is not going to accomplish anything is just a waste, as far as I am concerned. I just think that you ought to find out. There is a substantial possibility that the person already is infected. They may not think so but there is a good chance. So, it just would be I think very wasteful.

DR. GULICK: Dr. Wald, did you have a comment?

DR. WALD: Thank you. I guess my feeling is that people should be tested but not necessarily in the context of considering this added benefit of valacyclovir therapy. We know from other studies that clinical history of genital herpes is not always accurate. In fact, in the STD treatment guidelines laboratory confirmation of all genital herpes cases is currently recommended. So, it is

certainly recommended for the source partner to have laboratory documentation that they really do have HSV-2 infection.

In terms of the susceptible partner, given the experience in this population and finding that a substantial proportion of people who are concordant, not discordant, this is a situation which actually brings relief to a lot of couples, that the susceptible is already infected. Because of that, I think that testing should be encouraged, maybe not even specifically with the thought of initiating suppressive therapy but just because of the clinical discordant status.

DR. GULICK: Can I just make sure I understand this, the current recommendations for someone who has clinical symptoms of genital herpes is to undergo serologic testing?

DR. WALD: It is to undergo laboratory confirmation of the diagnosis and which test, whether it be a viral detection test or a serologic test, depends on the clinical presentation.

DR. GULICK: Okay, but that is for symptomatic patients.

DR. WALD: That is correct.

DR. GULICK: And either Dr. Wald or Dr.

Stone, other populations where it is routinely recommended to obtain an HSV serology currently?

DR. WALD: It is routinely recommended to serologically test those people who present for evaluation of STDs and request to be also evaluated for HSV.

DR. GULICK: Dr. Stone?

DR. STONE: Also, in the current version of the STD guidelines we say that serologic testing is useful for partners. We don't make a distinction between casual or regular partners. The thinking is, like Dr. Wald said, that the partner may already be infected and they are not going to get infected again so they don't need to worry about becoming infected. Also, they can benefit from counseling and learning to recognize symptoms and, you know, they themselves may become candidates for treatment. That is sort of the clearest indication for serologic testing in our guidelines.

DR. GULICK: Other comments? Dr. Guinan?

DR. GUINAN: There is a small problem with serologic testing in that it is type specific and if you are looking for HSV-2, then there is a certain percentage of genital herpes that is HSV-1.

In other words, it is not exactly that I know this person is susceptible because they are HSV-2 negative because if the source has HSV-1 and the partner is HSV-1 positive, then that person wouldn't need the drug. Do you see what I mean? Since a certain proportion of genital herpes is type 1, then doing type-specific antibody to determine a susceptible if you use only type 2, then you will have some degree of error in determining susceptibility.

DR. GULICK: Dr. Pazin?

DR. PAZIN: It is not nearly as traumatic to get HSV-1 genital herpes as it is to get HSV-2 genital herpes. So, I think that is not a major concern.

DR. GUINAN: Maybe not for you.

[Laughter]

DR. PAZIN: No, I can assure you that you can reason with those people, with the other ones it is more difficult.

DR. GULICK: Dr. Guinan, no comment? Your gestures say it all! Other thoughts on the serologic question? Dr. Fish?

DR. FISH: I mean, for the patient, they are not going to know whether they have 1 or 2 and

I am not sure I can follow that argument. What was my other comment? Oh, a total serology--I believe there is available serology that can detect both 1 and 2 so that might be a strategy that could be employed if the susceptible partner were going to be serologically tested.

DR. GULICK: Dr. Guinan, can you fill us in on that?

DR. GUINAN: I think I am going to say something controversial.

DR. GULICK: Good!

DR. GUINAN: I feel that women are disproportionately affected by this for lots of reasons, being more susceptible and having the poor outcomes of risk of transmitting this to a newborn. The male condom is not under the control of women and the treatment of the source, the male source is not under the control of women. Do you see what I mean? So, women are still very susceptible and what I think should be done is women should know their serostatus. In other words, women should know whether they are HSV positive or negative, especially for type 1 infection, and then let them know that they are susceptible and their partners, if they have known herpes infection, should be.

But this is what I have done and I have recommended off-label, and I am sure I will be put in jail some day but what I have done is to give young women valacyclovir who are in a relationship with someone because their male partner won't take it. So, I give it to the women to protect them. In other words, there is no data but it gives them something because they have nothing. They are madly in love and they can't resist. It is expensive and that is a big part, but the safety--so from my point of view, this is something that needs to be addressed in some way. In other words, women are susceptible and in trying to prevent perinatal herpes infection you need to prevent it in the woman. So, women's knowledge of their serostatus I think is extremely important and trying then to give them information about protecting themselves against acquisition of infection.

DR. GULICK: I think you are making important points. I don't want us to get too far away from where we are, which is what should be required in the label for valacyclovir for this indication.

DR. PAZIN: Clearly that is another study if you are going to be giving it to prevent

acquisition.

DR. GUINAN: It will never be done.

DR. GULICK: So, that was my point. So, interesting and provocative but maybe we should steer clear of it now. Dr. Kumar?

DR. KUMAR: Dr. Gulick, isn't the indication right now to prevent transmission to a susceptible person? Isn't that the indication for this drug?

DR. GULICK: Or to reduce transmission.

DR. KUMAR: To reduce transmission. So, that is why I am so confused. If the susceptible person is not susceptible, then the source person should not be taking the drug. So, I just find this whole question extremely unclear because that is the indication. It says we are giving it to prevent or reduce transmission. So, I think the susceptible person should be tested.

DR. GULICK: What I am hearing is consensus on this point but the practical world that Dr. Mathews describes is that not everyone has one partner that we can bring in for testing, and that is the clinical reality of this situation. So, I think most people around the table agree that serologic testing, if there is an appropriate

person to test, would be of great benefit and might actually exclude the need for this drug but there are many people in the real world where you will not be able to apply that. So, I guess that is our feeling on this issue. Okay?

DR. MATHEWS: Let me just give one example to make it very concrete. If a commercial sex worker who is HSV-2 seropositive has to require that their partners be tested in order to get this drug, you know it is not going to happen. So, I think or I would hope the sense of the committee is that, yes, it should be recommended to be done when it can be done but certainly not required, otherwise the people at greatest risk of transmission will not get access to the treatment.

DR. GULICK: I think that sums up the consensus very well. Let's move on, question number four, in your opinion--in your opinion, underlined--will marketing of valacyclovir for reduction of genital herpes transmission have an impact on the use of condoms and abstinence from sex during clinical HSV-2 outbreaks? Dr. Fletcher?

DR. FLETCHER: Well, I don't know is the easy answer but--

DR. GULICK: Question number five!

DR. FLETCHER: You said you wanted to get out early! But I do have two points. I guess one has to say I hope not, and I think that goes to Dr. Mathews' point about the confidence interval in the effectiveness in the reduction of transmission which, if my math is right, is 24 percent to 94 percent. So, the message needs to get out very strongly that, you know, yes, it works but the extent to which it works is really uncertain.

I think the second point that I want to make is that the benefit is not immediate. It seems from the data that Dr. Wald mentioned, it seems that one dose really does not convey a benefit. So, being on therapy, staying on therapy and using additional methods to prevent transmission seems to be the message that needs to get out. I think, great, to the extent possible efforts, aggressive efforts need to be made to ensure that people understand that other forms of protection need to be taken.

DR. GULICK: Dr. Sherman?

DR. SHERMAN: Does the sponsor have that slide that showed--I mean, we have data on this and it looked like condom use did go down. Was that statistically meaningful?

DR. GULICK: Or was that the agency that showed it? Dr. Smith?

DR. SMITH: We have that in our presentation. I think the applicant also showed a slide with the transmission.

DR. GULICK: Could we see that again? What slide? DR. SMITH: It was towards the middle, right at the end of efficacy. I think it is 26. Well, it is actually 27 and 28.

DR. HAVERKOS: Also 54.

[Slide]

Is that the one?

DR. GULICK: Can you walk us through this again, please?

DR. HAVERKOS: Basically, if you look at the reports of condom use in the month before study or baseline, remember, there are three groups, there is "never," "sometimes" and "always." As you see, we only have data on 725 of the 743 valacyclovir patients. It probably reflects the fact that they didn't actually collect some of this data until amendment I which was a couple of months into the study. But 32 percent said they nearly always used condoms and 51 percent said they never used condoms. That is 83 percent of the total.

For the other 17 percent, there was either no data or "sometimes." This was just for vaginal sex, 90-100 percent for "nearly always."

During the study itself you can actually calculate number of sex acts per month, and then each month you can calculate the condom use. If it is "nearly always" it is 90-100 percent. If it is zero, if they never used condoms for vaginal sex, anal sex or oral sex, it is never. Then, there is a group that gives you some data in between.

Then they take a median. So, in other words, there is eight months of data from many patients; there is five months of data for others if you take the middle month, so if it is all "nearly always" it is nearly always. If it is four "never" and two "sometimes" and one "nearly always" it is never. So you can actually go back and calculate these numbers. So, it doesn't actually translate into 90-100 percent across the whole study. It is a unique way of calculating condom use. But if you look at the baseline data and the vaginal use data from baseline through the study, you get a slight drop in "nearly always" and you get a slight increase in "never."

DR. GULICK: The denominator is changing.

DR. HAVERKOS: The denominators change, right.

DR. GULICK: Let's go to the sponsor on the same point and then I will take a couple more comments.

DR. COCCHETTO: Just a methodology caution on this. As you recognize, at baseline the information that is reported is the individual participant's recollection of activity from the prior month, whereas during the study it is actually diary card data that is being captured on a sexual contact by contact basis.

DR. GULICK: Thank you. Dr. Potter?

DR. POTTER: My one question was wasn't this during clinical outbreaks as opposed to during the full cycle?

DR. GULICK: It was assessed all throughout the study.

DR. POTTER: This was assessed but I meant the question. Wasn't it have an impact on the use of condoms and abstinence from sex during clinical outbreaks?

DR. GULICK: Oh, I am sorry, you are focusing on the question here.

DR. POTTER: Yes.

DR. GULICK: We have been a bit too broad, although that is also perhaps of interest. So, we have been considering generally in terms of looking at this data and the concern expressed here is currently during a clinical HSV-2 outbreak the recommendation is to be abstinent from sex, and will the marketing of valacyclovir actually impact that. So, let's focus on that specific question. Thanks for that. Dr. Englund?

DR. ENGLUND: I would just like to say that in my relatively limited by intense work with adolescents the answer is clearly no because they don't use condoms. They are not going to use condoms very much. We are trying hard, we really are but it is not going to change.

DR. GULICK: Dr. Stone?

DR. STONE: I would like to reiterate Dr. Englund's comment, common use is very low. Maybe I am a dreamer but actually the marketing could have a beneficial effect. Who knows about condoms, but the part on abstinence from sex when lesions are present, it could be that people haven't gotten this message that it is very important to not have sex when lesions are present. In a study alluded to by Dr. Corey and Dr. Wald, in the vaccine study,

during the course of that study people were counseled on condom use and also to avoid having sex when lesions were present and they actually reported that that declines over the course of the study, having sex with lesions. So, the effect could be, you know, in a good direction.

DR. GULICK: That is interesting. Dr. Guinan?

DR. GUINAN: I think it is really difficult to interpret these data without information on birth control practices of the women because some people do use condoms for birth control. In fact, the most committed users of condoms are those that don't want to get pregnant rather than for protection from disease. If these women changed their contraceptive us during the study they would maybe not do condoms. Do you see what I mean? So, it may have nothing to do with the study but something to do with the contraceptive practices. So, I think you can't interpret that data that Dr. Haverkos presented without knowing what the other contraceptive practice was.

DR. GULICK: Mr. Ebel?

MR. EBEL: Yes, I would like to comment on

the communications aspect of it because I think one of the things we know about counseling patients with herpes is that one of the areas where it is hardest for clinicians to spend time and do the counseling is precisely on impact on patient's sex life, and on risk reduction, and those kinds of things. I think the marketing of this and the increased awareness about the need for prevention and the awareness of a new intervention potentially could really have a positive effect in giving clinicians a more positive way to discuss this, in turn enabling patients to be more able to discuss it with their partners, and we know that that is a problem. So, the whole prevention thing at some point revolves around communication and this might help with that.

DR. GULICK: Dr. Pazin?

DR. PAZIN: When I look at these data, it suggest to me that these people put all their eggs in the pill basket. Really, when they go on a study, you know, if they didn't use condoms before they don't use them when they are on the study. Conversely, if they did use them almost all the time, they continue to do that. I think that it really doesn't have that much impact but I think

that having the availability of the pill will have the impact of making them disregard that other possibility of using the condom.

DR. GULICK: Let me try to summarize what we said here in terms of valacyclovir for prevention decreasing the use of condoms and abstinence during outbreaks. The consensus was that it could but recognizing that condom use tends to be low among people in general. We all agree I think, and would like to emphasize, that education is essential as part of the prescribing of this drug, putting valacyclovir in the context of other ways of avoiding transmission of HSV-2 and also recognizing the limitations based on the wide confidence interval once again. The fact that we are uncertain about the amount of benefit, that reduction is anywhere from 24-94 percent. Then Dr. Stone's point that this added education could actually be a benefit to tell people that active lesions are a time when they should be abstinent or use condoms.

Let's go on to the next question. Number five, although patients ion the registrational trial were treated for eight months, valacyclovir for suppression of transplantation of genital

herpes will likely be used for significantly longer periods of time. What additional studies would you suggest to evaluate the potential for longer-term adverse events, including resistance to valacyclovir?

We have touched on this several times over the course of the day. I think it was the consensus of the committee that this is a concern of ours, about the long-term safety, and the fact that duration, as was raised earlier in the day, is really not stipulated right now in terms of the indication.

Let's take that point first, duration of use here. What would we suggest as appropriate? Dr. Pazin?

DR. PAZIN: People are going to use it as long as they are at risk. I don't think that there should be that much of a duration emphasis--I think till their money runs out.

[Laughter]

DR. GULICK: Well, we heard a couple of interesting scenarios earlier today. Change of relationship, should that prompt a change in drug here? Or, what if the susceptible partner does seroconvert for HSV-2?

DR. PAZIN: Then you don't take it anymore.

DR. GULICK: There you go! Maybe this is painfully obvious here.

Specific studies to look at long-term adverse events? Dr. Englund?

DR. ENGLUND: I really think we need a pregnancy registration. We are used to using acyclovir in pregnant women. I personally don't know how much Valtrex is being used in pregnant women but I think that needs to be followed up because although I think there is no good data about immunocompetent adults ever getting resistant virus, I would be concerned potentially about a baby being infected with resistant virus, on a theoretical basis not based on what I see. I think that there is an obligation to follow the use of this through registration as opposed to a study.

DR. GULICK: Does the sponsor have data on valacyclovir in pregnancy?

DR. COCCHETTO: We do have some information. In concert with CDC and others we had a pregnancy registry that was initiated in 1984 with acyclovir and then subsequently expanded to include valacyclovir once that product was

initially approved within the United States. Dr. Alice White is the head of our epidemiology group who collaborated with Dr. Stone and others on that effort. I would be happy to ask her to comment on that briefly if you like.

DR. GULICK: Sure, that would be great.

DR. WHITE: Hi, I am Dr. Alice White, vice president of the epidemiology department at GlaxoSmithKline. As Dr. Cocchetto mentioned, we did initiate the pregnancy registry in 1984. It was really designed to look at major birth defects and compare the risk that might be observed with acyclovir used prenatally with risk of birth defects observed in the general population, through the CDC's birth defects surveillance system. As the first one approved that would be used widely in women of childbearing age, we felt it was important to look at major malformations. It was a short-term registry. Generally by the six-week visit we followed up to get birth outcome information. We have some results from that study on slides if you would like to see them. We terminated the registry in 1999 on the advice of our independent advisory committee because it was felt that the body of evidence about safety with

respect to major malformations was sufficient. Our enrollments had dropped off as clinicians and patients became more comfortable with use of the drug in pregnancy. So, we stopped it. Of course, at that point we weren't looking for things like resistance..

DR. GULICK: Would we be interested in seeing the data?

DR. ENGLUND: It is the acyclovir data, I don't need to see it; I have seen some of it. No.

DR. GULICK: Okay. Then, your other point I guess was about resistance in newborns as well.

DR. ENGLUND: Right. As we have said, I am not concerned about the transmission of resistant virus in the patients that we specify for use. I am concerned about the development of resistance in patients for whom this relatively low dose of drug is being used for a long period of time and who may have partners who are not who we want to give the drug to or who are themselves unrecognized as being immunocompromised. So, I would have some concerns about resistance for follow-up, not necessarily to change what we are doing today.

DR. GULICK: Is it fair to say--and this

came up earlier too--that follow-up of susceptible partners who seroconvert is pretty key, and it would have been helpful to see that in the study that was presented to know the clinical outcomes? We heard the resistance data I guess for ten of them, but also the clinical outcomes because of this concern that resistance could be a problem long-term, particularly as this gets into the population with widespread use. Dr. Wald, a comment on that?

DR. WALD: When we were designing the study we actually did not feel that that information to be very important because immunocompetent people heal their primary herpes whether or not they are given antiviral therapy. So, following somebody for a single episode and seeing it heal or not heal without any comparison really would not have, I believe, have provided us with any additional useful information to this point.

DR. GULICK: May I suggest that it would have been quite easy to put together and quite reassuring to know that the partners all had a normal course after receiving valacyclovir?

DR. WALD: That is correct but they didn't

have susceptible isolates.

DR. GULICK: That is helpful. Dr. Fish?

DR. FISH: I think that the package insert could just relate the fact of how long the trial lasted; that the experience was eight months, or whatever it is; and leave it to the provider and the patient to make the decision beyond that. I think it also adds to Dr. Mathews' point earlier about a recommendation for HIV testing because that is where we do see a not infrequent occurrence of resistance to acyclovir or the other agents that we have used historically. So, in that patient population we wouldn't necessarily want to be inadvertently treating them for suppression or otherwise and have the resistance issue come up.

DR. GULICK: Okay. I think we have covered that. Let's move to our last question. The primary endpoint in 3009 was the proportion of couples with clinical evidence of a first episode of genital HSV-2 in the susceptible partner. Would you recommend that primary endpoint in future studies? If not, what primary endpoint would you recommend?

We have really already considered this, haven't we? I guess the feeling was that because

of asymptomatic shedding and transmission seroconversion is a valuable endpoint, or the composite endpoint of both serological and clinical would be--I am trying to speak for everyone--it would be our consensus that that would be even a better endpoint than clinical alone. Comments? Dr. Pazin?

DR. PAZIN: I think they should be sort of co-equal endpoints in the sense that I am interested in how many people develop clinical disease, recognizable and documented, confirmed. I am also interested in serologic conversions. I think, you know, pretty much the way this study did it, should be sort of co-equal endpoints, that they should both be incorporated.

DR. GULICK: Well, co-endpoints is tough. You could have a composite including both or you could make one your primary and one your secondary. But you are saying that they both tell you important information.

DR. PAZIN: Yes, important information.

DR. GULICK: Any other thoughts about that? Yes, Dr. Englund?

DR. ENGLUND: I would just say I think the primary should be serologic and the secondary could

be the clinical.

DR. GULICK: It certainly would make studies easier to do.

DR. ENGLUND: Well, it would also give uniformity. You know, with frequent serology it would give uniformity to Australia and eastern Europe, things like that.

DR. GULICK: We are all for uniformity in Australia and eastern Europe. Dr. Mathews?

DR. MATHEWS: I had a comment on a different matter.

DR. GULICK: Okay. Any other comments on endpoints? We have pretty much covered that I think. So, last couple of matters to think about.

DR. MATHEWS: I have a concern about the dose appropriateness for this indication. Because the risk reduction, depending upon what the endpoint was, varied from 0.5 to 0.75, it is clearly not zero. If you were to restrict this analysis to people who are at high risk of transmission, namely, some of those characteristics would be recently acquired infection, relationships of short duration, very frequent intercourse and other factors, a lack of use of condoms, all of these, what do we know about how well the drug at

this dose works in the high risk setting? That is to say nothing about other populations, for example the dose in immunocompromised or where the predominant form of contact is not vaginal intercourse, and so on. So, I think this is an area for additional study to examine the dose and to try and identify settings in which people at high risk for transmission can be studied because, this population, really the way it was constructed to make the study feasible was skewed towards relatively lower risks of transmission I think.

DR. GULICK: Other comments on other issues that people would like to make? Dr. Birnkrant, how did we do?

DR. BIRNKRANT: Very well today. We got a lot of useful information.

DR. GULICK: Great! So that brings us to the end of the meeting. I would like to thank the sponsor and the agency for their presentations today, the committee for a lively, provocative and far-ranging discussion, and we will close the meeting now. Thanks.

[Whereupon, at 3:15 p.m.., the proceedings were adjourned.]

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