ONCOLOGY DRUG ADVISORY COMMITTEE

Monday, November 16, 1998

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P R O C E E D I N G S: 8:30AM

DR. DUTCHER: Good morning. This is the Oncologic Drugs Advisory Committee, and we are here just for today to discuss two agents. First, I would like to go ahead and introduce the members of the committee, and then we will be reading the conflict of interest statement, and then we will proceed with the open public hearing. My name is Janice Dutcher. I am from Our Lady of Mercy Medical Center, New York Medical College in New York, medical oncology.

[Introductions were made.]

Agenda Item: Conflict of Interest Statement

MS. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard 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 for the meeting and all financial interests reported by the participants, it has been determined that all interests and firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for a conflict of interest at this meeting, with the following exception:

Dr. Kim Margolin has been a granted a waiver which permits her to participate fully in all matters concerning DepoCyt. A copy of the waiver statement may be obtained by submitting a written request to the FDA's Freedom of

Information Office, Room 12A-30 of the Parklawn Building.

In the event that the discussions involve any products or firms not already on the agenda for which an FDA participant has 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 involvement with any firm whose products they might wish to comment upon.

That is my last conflict of interest statement for this meeting.

Agenda Item: Public Comments

DR. DUTCHER: Thank you.

We do have some speakers for the open public hearing. We would ask you to come up to the microphone. Please identify yourself, and please let us know if you have any sponsorship from the pharmaceutical sponsor. We will start with Ricardo Garcia.

MR. GARCIA: Good morning. My name is Ricardo Garcia. I come here to tell you about the Panretin Gel that helped me. I am a volunteer. I come here on my own. I was reimbursed by Ligand. I have lesions over extensive parts of my body, on my arms and legs, and most of them were about

dime size to quarter size. The biggest one was over my hand, and it was kind of bubbled up. I had one on my chin. There were a total of about 15 lesions all over my body. They were black and blue. They kind of singled me out. So I kind of wore a lot of long sleeves and long pants all the time.

When this gel came out, I had radiation done on a couple of them, and it just did not work, and the gel just took it away within three weeks of using this gel.

Besides the emotional issues that the lesions did to me, the physical pain from the KS that it gave me, from the inside out, the gel seemed to kind of calm it down and controlled that pain. I used the open label for about, I think, eight weeks, and I saw a difference within the third week I started using it.

Right now, I have two lesions left, and the only reason I have them is because they cut the study on me, and they pulled the medication away from me, but I think that if I could get the gel back, they would go away.

DR. DUTCHER: Thank you.

Next we will hear from Mark Mischan.

MR. MISCHAN: Good morning. My name is Mark Mischan. I am here from San Diego. I am here voluntarily, and I would like to speak to the benefits that I received personally from the use of Panretin gel. I have no

relationship with Ligand Pharmaceuticals, other than for their reimbursement of my travel-related expenses. In January of 1982, in addition to a low T-cell count, Kaposi's sarcoma was my AIDS-defining opportunistic infection. In June of 1995, I requested radiation treatment involving three of the lesions on the soles of both of my feet because of the associated pain and discomfort that I realized from those.

The radiologist advised against additional radiation treatment because of the numbers of the lesions and the locations on the other sites of my body. I chose not to resort to other aggressive and invasive forms of treatment such as the chemo therapeutic agents in the KS lesions. After consulting with my primary provider, I chose to participate in the Ligand clinical trial number 1057, which is from the University of California in San Diego.

While I was in the Ligand study, I was drug-naïve to antiretroviral treatments. I did not begin any antiretrovirals until December of 1996. My only medication I was using at the time was prophylactic measures. I used Bactrim septra, which I still use today to prevent the development of PCP.

My personal experiences with the use of the Ligand gel were very positive for me personally. I had no extraordinary physical discomforts, other than minor skin

irritations. I felt that the at-home use of the product was very safe. It was easy. It was very convenient. It also allowed me to use the product in other public situations and remain somewhat confidential about the use of it. So it was easy.

My treatments totaled about 15. I treated eight. I used two as controls. I chose the lesions that were very physically noticeable and that I believed inhibited my ability to be socially active. I had a couple of lesions on the wrist, which disappeared anywhere from 8 to 12 weeks from when I noticed. I had one on my neck and one in my armpit and the groin.

Well, I used the gel. What I did notice was there was a reduction in the visible pigmentation. Most of mine were probably -- mine started out to be flat. They were never really grossly raised. But they were usually a dark purple. Now with using the gel, there was a lightening of the pigmentation. On any of those that I treated, there has never been a redevelopment of any of the pigmentation. There was a reduction in the size and the shape, which for me was very gratifying. There were times I actually had to go to seminars to learn how to apply makeup so I could go out and be physically active out in public.

Because I have developed additional new lesions, aside from the ones that I originally manifested, I have an additional

need for the Panretin Gel. I still refuse to use any invasive therapies, chemotherapeutic agents. So for me, I am very hopeful that we can get approval of the Panretin Gel. My primary care provider is supportive, and he would allow me to have access if it is approved. So I do have a need.

I think there are many people in the HIV/AIDS community who are suffering from the emotional scars and from the health risks associated with KS tumors, and I really hope that we can receive approval of this drug in the near future, because there is a definite ongoing need.

Thank you very much.

DR. DUTCHER: Thank you. Could you answer one question?

DR. ABRAMS: You mentioned lesions on the soles of your feet. Did you apply the gel to those lesions, as well?

MR. MISCHAN: No, because at the time I did not have access to the gel. So on the dates -- I actually got my -- through a skin biopsy. I live in San Francisco. That is where I received my AIDS-defining condition. I had the radiation in June 1995. So the radiation was received prior to having access to any of the gel, and even before I had access to the gel, I was not using any antiretrovirals. So for me that was a very definite marker. I could see the benefit from the use of that.

DR. DUTCHER: Thank you.

Shon Johnston?

MR. JOHNSTON: Good morning. My name is Shon Johnston. I am from Los Angeles, California. Ligand Pharmaceuticals is not paying me to be here today. I am here on my own free will. However, they are reimbursing me for my travel expenses. Otherwise, I could not be here.

I was first diagnosed with Kaposi's sarcoma about four years ago. Since that time, I have done interferon injections, chemotherapy, and radiation treatments. Although the chemo and radiation treatments stopped the progression of the lesions, they did not take the lesions away. So I still had lesions on approximately 80 percent of my body. I had well over 100 lesions.

I began using the Panretin Gel in January of 1997, and I have continuously used it ever since. After seeing the positive effect of the gel on the original six test lesions, I began using it on the other lesions on the rest of my body, and I found it to be very effective, as only about 5 percent of those lesions still remain. The only side effect I have experienced from it is the itching and a little inflammation, which quickly subsides after a while, from using the gel.

I was not using any of the medicines or whatever during this time. So there was no influence from the

medicines on this. So I am very certain that it was from the Panretin Gel that the lesions have gone away. The ones that have gone away, I have stopped using the gel on them, and none of them have returned to this point.

Since using the gel and the lesions have disappeared, my emotional state and everything has greatly increased because of my physical appearance. For the first time this summer, I was able to wear shorts outside, and in Los Angeles it gets pretty warm in the summer and wearing long pants can get a bit uncomfortable.

I would sincerely hope that this gel is approved, because it has made a remarkable difference for me, and I am sure that it will be a great help for other people, too.

I thank you for your time and consideration.

DR. DUTCHER: Could you take one question?

MR. JOHNSTON: Sure.

DR. ABRAMS: Did you imply then that you had put the gel on lesions that had been previously flattened or disappeared -- not disappeared, but previously flattened from another therapy, and those went away?

MR. JOHNSTON: Yes, those disappeared, too.

DR. DUTCHER: Thank you.

Thomas Kennedy?

MR. KENNEDY: Good morning. My name is Thomas Kennedy. I am from upstate New York. I am here to share

with you the gratifying effects I have had with the use of Panretin topical gel. Ligand has not paid me to speak on their behalf, although they have paid for my travel expenses. I am here -- I am glad to volunteer my time to speak to you about the benefits I had with Panretin gel.

A few months into the year 1995, I learned I had the HIV-related disease Kaposi's sarcoma. I then started treatment with Dr. Zale Bernstein(?) at Roswell Park Cancer Institute. He put me on a protocol which consisted of going to Roswell three mornings a week and having a vitamin A treatment. Several unpleasant side effects I had were weight gain, severe headaches, and nausea. Although I think this treatment stopped the progression of my case, I still had lesions on my face, neck, arms, and legs.

The only other person besides my doctor that knew of my illness was my wife. Having these noticeable lesions was a constant battle. It was becoming unbearable trying to keep the secret. These obvious lesions on my body were becoming more and more problematic. I maintained a 40 to 60 hour work week as an auto worker where I used to shower and change with coworkers before these lesions appeared. I had to modify my work routine to keep my illness confidential.

This was especially important to me because I worked with my father and brother. I also had to change a lot in my social life, because I enjoyed a lot of outdoor

activities before I became ill. I was an avid water skier and also spent a great deal of time with my family at a beachfront cottage. Coping with these lesions and the fear of having them seen brought me to a very low point in my life.

In October of 1996, I started another protocol at Roswell Park Institute. On the new protocol, I went from three clinic visits per week to eventually one per month. Not having to go to clinic three times a week was a great relief. My life was starting to feel normal again. This time the protocol consisted of my using Ligand's Panretin gel three times on six different lesions. Using the topical gel was a lot easier, because I could use it in the privacy of my own home and apply it to myself.

Approximately one month after I began using the gel, I noticed a remarkable change in a very large and risen lesion on my neck. It began to flatten and disappear. At this time, my other lesions started to fade, too, and eventually all disappeared.

To date, I have no visible marks or scars from the KS. The disappearance of the lesions has given me a new outlook on living with Kaposi's and HIV. I was able to resume all of my normal activities, not fearing changing showering or changing at work, water skiing, or summer activities with family and friends. Ligand's Panretin gel

changed my life physically and emotionally. I hope more people suffering from KS can experience the success I have had.

DR. DUTCHER: Thank you. Thank you very much.

We appreciate you all coming to share your experiences. We now have two letters to read from people who also want to make a comment.

MS. TEMPLETON-SOMERS: To whom it may concern, I wish to share my experience using Panretin gel, but I first wish to state that Ligand Pharmaceuticals is not paying for my endorsement. I volunteer this information because before using Panretin gel, I have no need to wear an AIDS awareness ribbon. A cursory look at my face and body left no doubt that I was a person living with AIDS. My Kaposi sarcoma lesions were rudely evident and boldly disfiguring. Although only six lesions were to be studied, I had many more than that number several places on my body, face, limbs, and trunk, and I treated all 30-plus with Panretin gel. I had failed interlesional therapy, and I was allergic to systemic lipid therapies. Cryogenics did not tempt me, and radiation was a resource that I hoped to save against the day when I might need it more.

However, it seemed as if my lesions were propagating like rabbits, encroaching upon my complexion with a menacing surety. This was a topical treatment, not

invasive at all. Could it possibly work? What did I have to lose?

Once I began Panretin gel, any lesion that was raised flattened. All lesions have either faded appreciatively or resolved completely. Any reminder of my KS that remains is only dimly similar to what was a glaring indictment of an out-of-control situation. The three lesions that remain visible in any capacity look more like birthmarks now.

Panretin gel is a marvelous advance for the treatment of KS, and I would encourage you to make it available to the public as soon as possible. I have my body back and I can once again recognize my face reflected in a mirror. Panretin gel works.

Thank you for your attention to these matters.

Sincerely, Ronald Richards, New York, New York.

The second letter:

I am writing this letter to explain how Panretin gel has helped me with my KS lesions over the last 17 months approximately. This letter is being written voluntarily. Ligand has not paid me for this letter or offered any incentive to motivate me to write this letter. I am writing because I truly believe that Panretin gel has greatly helped my KS condition.

About a year and a half ago, I found out that I

had KS. Initially there were only two lesions I could see, but after closer inspection by my doctors and myself, I noticed several -- two to three dozen -- smaller spots. X-rays revealed there were no lesions in my lungs.

Most of these lesions were on my feet and back. I had shingles a few months before, and the scars left by the outbreak were a central spot for the lesions.

After being referred to a specialist, I was enrolled in the Ligand study, and only three or four weeks after finding out I had KS. Therefore, I cannot really tell you had the program not been available how my life with KS would be. I can tell you that the positive reaction I have experienced on the gel has helped give me a sense of hope that I would look better.

Five spots were treated for the study. I also used the gel on four or five other spots. The spots used for study were treated one to two times a day. I did not treat the other spots quite as often -- once every two or three days.

I have had radiation treatment on three or four spots. It was a while ago, and the spots were quite close together. These sports were on my feet and made walking difficult. Radiation was the quickest way to relieve the pain. It worked very well but left brownish spots where the KS spots were. Not a big deal on my feet, but I would not

want these spots anywhere more visible.

I had two lesions burned off with liquid nitrogen. This was quick, but a little traumatic. Panretin has provided an easy option. There is no pain, trauma, or residue scarring with the spots I have been using the gel on.

The benefits I have had from Panretin are primarily cosmetic. The lesions treated flattened out very quickly and over time the five sports involved in the case study have nearly disappeared. There is a small amount of reddish irritation around the spots I have been treating, but this goes away in one day if the treatment is stopped. The flattening showed me right away that I was getting results. My skin felt better to my touch. This was a psychological plus for me.

Feeling I look better, or at least more like I am used to looking, has of course made my emotional situation better. I think most of us are at least a little vain. I am no exception. So I feel better when I feel I look better.

In closing, I can sincerely say I am grateful for the treatment option Panretin has provided me with, and I am very pleased with the results. I can be contacted for further input, if necessary.

This is Paul Curwin, from Vancouver, British

Columbia.

Copies of the letters from the public are available for your inspection at the registration desk.

Thank you.

DR. DUTCHER: Thank you.

I would just like to introduce one more member of the committee. Michael Marco is here as a patient representative.

If there are no other comments, no other public comments, we will proceed with the sponsor's presentation on Panretin.

Agenda Item: Ligand Presentation

Agenda Item: Introductions and Background: Howard T. Holden

DR. HOLDEN: Thank you very much, Dr. Dutcher, and good morning. My name is Howard Holden. I am the vice president of regulatory affairs and compliance at Ligand Pharmaceuticals.

On behalf of Ligand Pharmaceuticals, I would like to say that we are pleased to be here today to present the results of the developmentive program for Panretin gel.

Indication that we are seeking for this product is for the first line topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma. Today we will present the data from two phase 3 randomized vehicle control

trials which demonstrate that this product is safe and effective for treating patients with this disease.

The active ingredient in Panretin gel is alitretinoin, also known as 9-CIS-retinoic acid. The retinoid, a derivative of vitamin A, is a natural hormone and, as such, is found in low levels in the plasma of untreated individuals. The formulation of Panretin gel that was utilized in the clinical trials was an alcohol-based gel with a concentration of 0.1 alitretinoin.

The IND initiated the phase 1,2 trials was filed in March of 1994. In January and October of 1996, after discussions with the agencies on the design of the pivotal studies, the phase 3 protocols were filed to the IND. Orphan drug designation was obtained in March of 1998, and the NDA was filed in May of this year. After the initial review of the NDA, the Oncology Division gave the NDA a priority review.

We would like to thank the division for the assistance they gave us during the development of Panretin gel, and we would like to acknowledge the swiftness with which they have reviewed the NDA. In addition, I would like to give a special note of appreciation to Amy Chapman, the FDA Consumer Safety Officer, who has worked closely with Ligand on this NDA. Thank you.

The agenda for the presentations on behalf of

Ligand in support of the application are outlined in the slide. Dr. Steven Miles, a medical oncologist at UCLA, will present an overview of the disease. Dr. Richard Yocum, who is the medical monitor for the clinical trials, will review the efficacy data from the pivotal studies. Dr. Steven Reich, the senior vice president of clinical research, will present the safety data, and we will hear from two clinical investigators who participated in the clinical trials: Dr. Barbara Melosky, a medical oncologist at the British Columbia Cancer Agency, and Dr. Neil Bodsworth, director and research coordinator at the Taylor Square Private Clinic Sydney. They will discuss their personal experience on the clinical benefit obtained by patients who were treated with Panretin gel.

For the benefit of the committee, Ligand has provided a printout of the slide presentations. Slides in the presentation can be referenced by the number in the lower right-hand corner of the handout.

In addition to the investigators, we also have here today Dr. Thomas Fleming. He is the professor of biostatistics at the University of Washington and has participated with us in analysis of some of the data of the trial.

Now I would like to turn it over to Dr. Steven Miles, who will provide an overview of Kaposi's sarcoma.

Agenda Item: Overview of Kaposi's Sarcoma: Steven Miles

DR. MILES: Thank you, Dr. Holden, and good morning, committee members.

My task this morning is to provide some information on the devastating disease which you have already heard about from the patients and help you understand the spectrum of disease and place this new topical therapy in the context of other therapies.

Kaposi's sarcoma is by far the most common malignant complication of HIV. Patients who have HIV are approximately 40,000-fold more likely to develop Kaposi's sarcoma than those who are HIV-negative. Because it is clearly and readily recognized by dermatologists, oncologists, and other persons familiar with HIV infection, it originally represented approximately 18 to 20 percent of all new AIDS diagnoses back in the early 1980s. It has now fallen to approximately 9 to 10 percent of all new AIDS diagnoses. This has been relatively stable since 1991. This is in large part because we now diagnose most of these cases with either wasting or low CD-4 counts based on HIV serologies. It still is a significant cause of morbidity and occasional cause of mortality.

The disease presents in two contexts: one, in untreated HIV infection, where control of HIV replication

and immune deficiency secondary to that is manifest -- so this is in largely untreated individuals; and, second, in those individuals who are on HIV therapy or who already have a diagnosis of HIV during times of opportunistic infections or under situations in which HIV therapy is poorly controlled.

We think that this occurs because there are a number of cytokines which are exacerbated during opportunistic infections, some of which are known mitogens for the cells that are derived from these, including basic Fibriglos(?) growth factor, TNF, IL-1, IL-6, and others. In addition, we know that HIV proteins themselves may play a role. One of the proteins, the transactivating protein, tat, can directly increase the proliferation of these cells in culture. Finally, we know that there may in fact be poor control of the human herpes virus, HHV-8, which may be pathogenic in the cause of this disease.

As I mentioned, there is a spectrum of disease. You see patients with, for example, plaque-like lesions on the forehead, small nodular disease here on the nose, small multiple nodules here in the area of previous radiation therapy, large nodular disease here on a patient's chest, and finally tumor-like growth involving an entire leg.

Some of these can be very challenging. For example, these are occurring in a patient who has already

had radiation therapy to the nose. So treatment with other forms of treatment than Panretin gel would be very problematic. Similarly here, in a patient who has already had radiation therapy, this can be problematic.

Treatments are largely divided into two groups: local therapies that we use for cutaneous disease and systemic therapies that are used for patients with life-threatening disease, usually pulmonary involvement.

If we focus on topical treatments, you can see that there are a number of different therapeutic options for physicians at the current time. These include everything from liquid nitrogen all the way down to surgical excision. These vary significantly in their need for specialized services. Some of these are relatively inexpensive and easy to implement; others, such as radiation therapy or laser therapy, require very specialized equipment. They also vary in their effectiveness and in the overall cutaneous result. As the patients noted, for example, radiation therapy often leaves a pigmented lesion behind, and this may not be any better than what the original lesion was. In addition, you can have scarring that results from inappropriate use of liquid nitrogen. So there is a significant amount of operator error that may occur.

There is a continued need for new therapies in KS. Many of the physicians think that our current therapies are

unacceptable, and as a consequence they leave patients untreated. As you heard from many of the patients today, in fact, they were not treated until they were referred to a specialist in this disease. This can cause significant morbidity and psychological harm to a patient.

In addition, there is a widespread notion that if you control HIV that all of these lesions will go away, and while that certainly may be true for patients with early stage 1 or stage 2 cutaneous disease, that is not true for all of the patients. So many patients are left untreated by their HIV physician. Finally, widespread treatment, as some of the patients talked about today, is very problematic. It requires multiple trips to the physician and is largely impractical.

The advantages of a self-administered agent are significant. Number one, under the physician's supervision the patient can self-administer the drug in the privacy of their own home. They do not have to make trips to the physician's office. Second, they can be taught to recognize early lesions and to intervene where more rapid resolution of the lesions may in fact occur.

Finally, the patient can titrate the drug treatment as tolerated. Patients vary significantly in their tolerance of the drug. There are different tolerances based on where the drug is applied on the body, and the

patient is probably the best person to assess what their own tolerance is for this.

I have been involved in the development of this drug since very early on. I would just like to share with you a couple of pictures here from some representative situations. This is a patient who has a large nodular lesion on the chest. After approximately 10 weeks of therapy, you begin to see some clearing here, flattening of the lesion. It is actually larger in size than the original area because there is erythema around from the drug.

At follow-up you see a crusting scaling area here of prior treatment. All of the lesion is gone. The large nodule is now completely disappeared. On biopsy of this, you can see that there still is patch stage Kaposi's sarcoma here. So although we look visually and we think that this is gone, there still is patch stage Kaposi's sarcoma. There is no cellular infiltrate here to indicate an inflammatory response.

In contrast, from the same patient, same time course, you see a smaller lesion. Here again with the large amount of erythema and exfoliation, small pink lesion left after treatment. This is biopsy, and now there is no evidence of disease. So the complete resolution that is pathologically confirmed through topical therapy.

It is important to keep in mind that we need to

treat HIV as well as prevent opportunistic infections. We know that HIV replication can be involved in facilitating and increasing replication of Kaposi's sarcoma. So this needs to be borne in mind by all treating physicians.

In conclusion, topical Panretin gel represents a new direction in the therapy for patients with Kaposi's sarcoma. It is the only self-administered agent that is well-tolerated and appears to be effective, and it provides an alternative to other forms of topical treatment.

At this time, I would like to conclude and introduce Dr. Richard Yocum from Ligand Pharmaceuticals who will talk about the efficacy from the phase 3 controlled trials.

Dr. Yocum?

Agenda Item: Panretin Gel Efficacy Data: Richard C. Yocum

DR. YOCUM: Good morning and thank you for the opportunity to present the design and efficacy results of the phase 3 clinical trials of Panretin gel and Kaposi's sarcoma.

I will begin with a review of the design and scope of these studies and then characterize the main eligibility criteria and the enrolled study patient population. This will be followed by a review of the efficacy endpoints and the results of those efficacy studies analyses, and finally

a summary and conclusions.

In the phase 1-2 clinical trials -- and there were only 115 patients at nine U.S. study centers -- studies demonstrated that Panretin gel has activity in AIDS-related KS. Although there was no discernible dose-response relationship, it is noteworthy that all three clinical complete responses occurred at the highest -- .1 percent -- concentration of gel. The gel application had no effect on the range and frequency of detection of plasma 9-cis-retinoic acid levels and was generally well-tolerated over a median duration of 14 weeks. These findings provided justification for further study in the phase 3 clinical trials.

Beginning then with a review of the design and scope of these studies, there were two phase 3 clinical trials. These studies were nearly identical in design, with a couple of differences. The North American study, protocol 1057T-31, enrolled 268 patients in 35 enrolling study centers in the United States and Canada and dosed patients at .1 percent TID escalating to QID after two weeks. The international study, protocol 1057-503, enrolled a total of 134 patients at 22 centers in the United States, Europe, and Australia, and dosed patients at a fixed dose of .1 percent BID. Both studies included provisions for reduction in the frequency of application in the event of toxicity.

I should note that the international study was terminated early after a protocol-defined early stopping rule was satisfied, and most of the data that I will be showing you today is based on the 82-patient interim analysis data set.

This schematic of the North American study shows that following screening, eligible patients were randomized in a blinded fashion, one to one, either to blinded Panretin gel treatment or blinded vehicle treatment. The protocol contained, as suggested by the FDA, various crossover elements for patients progressing during the initial blinded treatment. They were permitted to cross over, still blinded, to the alternate blinded treatment arm.

At 12 weeks, or longer in the event of progression or response not yet confirmed over four study weeks, patients became eligible for the open label phase of the study.

In the international study, patients were again randomized in a blinded fashion, one to one, to either blinded Panretin gel or vehicle gel, and at 12 weeks became eligible for the open label follow-on study.

I will now present the main eligibility criteria for these phase 3 studies. These criteria required adults to be HIV-positive with biopsy-proven KS, a Karnofsky status of at least 60 in the North American study or an ECOG of 0,

1, or 2 in the international study. Patients must have had sufficient lesions to qualify as cutaneous index lesions. In the North American study, six lesions were designated as index lesions, of which three must have been raised, each lesion measuring at least 10 millimeters or present for at least 30 days. In the international study, a minimum of three to a maximum of eight lesions were designated, each lesion measuring at least 2 by at least 10 millimeters in diameter. Lesions anywhere on the body were eligible for designation as index lesions and were selected to be representative of the patient's overall cutaneous disease. Patients with visceral disease were excluded only if it was anticipated that systemic therapy would be required during the course of the study.

The criteria required acceptable organ function and absence of active serious infection. These studies of a topical therapy for a cutaneous KS could not reasonably restrict or control concurrent antiretroviral therapy, given the very dynamic and rapidly evolving state of knowledge about optimal antiretroviral therapy. However, all concomitant medications were carefully recorded for later analysis.

These criteria were purposely designed to enroll the broadest population of patients with Kaposi's sarcoma, and a characterization of the enrolled study population

shows this to be true. Looking at the baseline of extent of disease for the 268 patients in the North American study and the 82 in the international study, we see that the duration of disease of KS from diagnosis to entry in the study was just over 1 year in the North American study where this information was available. Visceral involvement was known to be present in 12 and 16 percent of patients in the studies.

Using the ACTG's tumor, immune system, and systemic illness staging system, 72 and 87 percent of patients had at least one poor risk factor. Approximately one-quarter of patients had CD4 count in the low range of 0 to 50, and in the North American study, 37 percent had more than 50 cutaneous lesions. The aggregate area of the indexed lesions was on the order of 700 square millimeters.

These data show that the enrolled study patient population was not limited to patients with early cutaneous only disease but, in fact, included patients with a wide-ranging extent of cutaneous disease, a range of immunodeficiency, and even some patients with visceral involvement.

The blinded randomization in the North American study resulted in 134 patients randomized to each treatment group. These treatment groups were characterized and compared for a wide array of baseline characteristics and

found to be well matched for each. In particular, with regard to prior anti-KS therapy, the treatment groups were well matched, with about two-thirds of patients having received at least one prior therapy. Also, with regard to baseline antiretroviral therapy, the groups were well matched with about two-thirds of patients on at least three antiretroviral agents. The treatment groups were also well matched with regard to the presence or absence of a protease inhibitor.

Similarly, in the international study, with 36 patients assigned to Panretin gel and 46 to vehicle in the interim analysis data set, the treatment groups were well matched for all characteristics, including prior anti-KS therapy present in about one-third of patients and baseline antiretroviral therapy with approximately three-quarters of patients having been exposed to three or more agents, and again, this was also true when considering the presence or absence of a protease inhibitor.

Before I review the efficacy, I would like to now present the efficacy endpoints for the studies, and I would like to point out for both phase 3 studies and the phase 1-2 program that the response rate, that the primary endpoint, efficacy endpoint, was the same and consisted of the response rate, using the ACTG criteria as applied to index lesions with the patient as the unit of analysis. A number

of secondary efficacy endpoints were employed, including a physician's global assessment in the North American study, a physician's subjective assessment in the international study, and patients' own self-assessments of their course of disease, including a quality of life questionnaire in the North American study and a patient's subjective assessment in the international study.

Recognizing the unique challenges of evaluating a disseminated cutaneous neoplasm, the Oncology Committee of the ACTG published in 1989 a standardized set of response criteria and a staging system for KS. These remain the only published, standardized, and widely accepted criteria for KS and have served as the basis of approval of drugs for the treatment of AIDS-related KS. The criteria may be easily applied to the evaluation of topical therapy, because they are in fact a set of dual-response criteria, one involving the patient's overall extent of KS disease and then a second based on the group of bidimensionally measurable designated index lesions. It is the second criteria in the index lesions which is so easily adaptable to topical therapy, in which the assessment is limited to only those cutaneous lesions being treated.

The lesions are assessed for height and also for area, using bidimensional diameters, and under these criteria patients may be classified as a responder according

to area or height in which a partial response requires at least a 50 percent or greater reduction in area and a response by height is constituted by a 50 percent or greater reduction in the number of raised lesions.

Before I present the efficacy results, I would like to point out that all of the efficacy results I will be showing in this presentation are based on the intent-to-treat population of patients, including every patient that was randomized to study drug treatment. Applying these criteria to the phase 3 studies yields the following response rates: in the North American study, a 35 percent response rate to Panretin gel versus 18 percent vehicle, with a p-value of 0.002, using the Fisher's exact test, and in the international study, where the perspective protocol specified interim analysis of the first 82 patients was done, the response rate was 42 percent on Panretin versus 7 percent on vehicle.

This satisfied the protocol-defined early stopping rule. However, during the conduct and verification of the interim analysis, enrollment was not suspended, and an additional 52 patients were enrolled. When the blind was broken for the full 134 patient analysis, the interim analysis results were reinforced with a 37 percent response rate on Panretin versus 7 percent on vehicle, and a p-value of 0.00003. Issues regarding the interim analysis,

specifically regarding the appropriate application of the O'Brien and Fleming(?) rule, were identified by Ligand and communicated to FDA. I will be saying more about these issues in a few moments.

It is noteworthy that during the open-label phase of the North American study, the 35 percent response rate seen during the initial blinded phase increased for patients who were randomized to Panretin to 49 percent during the open-label treatment, and if we look at all 184 patients who were entered in the open-label phase, the response rate was 49 percent. This increase in response suggests that the full anti-tumor potential of Panretin gel was not realized during the initial 12-week initial blinded study phase.

The results for the crossover phase in this study were noteworthy in that -- and as you recall, patients progressing were permitted to cross over to the other blinded treatment arm -- only two patients crossed over from Panretin to vehicle versus 15 patients crossing over from vehicle to Panretin gel. These 15 patients progressed over a median time of 47 days on the vehicle treatment and at the time crossover had a resetting of the index lesion baseline, with 4 of the 15 patients then responding to Panretin gel over between 14 and 35 days. This means that patients who had a 25 percent or more progression, after crossover then experienced a 50 percent or more improvement over an even

shorter time than they had progressed. The ability of Panretin gel to rapidly reverse progression provides compelling evidence of its anti-tumor activity.

Subgroup analysis was performed on phase 3 studies and consistently showed the benefit of Panretin gel treatment, regardless of demographics, the area of the index lesions, the number of raised lesions, the performance status, opportunistic illnesses, the CD4 count, concurrent antiretroviral therapy or other antiviral therapy, and the extent of prior anti-KS therapy.

This graph shows the percent of patients responding in the North American study versus the extent of concurrent antiretroviral therapy. With Panretin gel in red and vehicle gel in yellow, one can see that the response rate for Panretin gel exceeded that for vehicle in every category in which response was observed for either no concurrent therapy, one, two, three or more antiretroviral agents. The same was found to be true when considering the absence or presence of a protease inhibitor.

The same analysis for the international study showed the same results, with once again Panretin in red, response rate exceeding that for vehicle in every category in which response was observed, with nearly all patients in the two agent or three or more agent categories. For both the North American and international study, an adjusted

statistical analysis for the extent of concurrent retroviral therapy showed a statistically significant effect of Panretin gel.

Showing here the percent of patients responding versus prior anti-KS therapy with the North American study in green and the international study in lavender, it can be seen that responses were uniformly observed in patients who had had no prior therapy for KS, patients who had prior systemic therapy, and even in some patients who were refractory to prior systemic therapy, including refractoriness to systemic cytotoxic agents and interferon.

The minimum time to response was largely determined by the first on-study assessment, which occurred at week two, and was found to range 14 to 15 days. The median time to response, if we look only at the initial blinded phase, was approximately one month. However, as I have shown you, responses have continued to accrue with longer durations of therapy, and in order to get a better appreciation of the time to response, we turned to a Kaplan-Meier analysis, here showing for the North American study the percent of patients who respond versus the time to response, with the vehicle gel patients in white and the Panretin gel patients in yellow, as they are followed through the initial blinded phase and then into open-label therapy.

The Panretin curve, the responses continue to accrue on Panretin as a function of longer treatment durations, and following these patients into open-label therapy, we see that at 191 days, 75 percent of patients who are still on study are projected to respond, and the time to response was consistently shorter for Panretin gel compared to vehicle, with a p-value of 0.0001 using the Log Rank Test.

Although there were fewer patients in the international study, the results were the same, with Panretin gel favored over vehicle.

It is difficult to determine the true duration of response, because there were, in fact, so few relapses observed. In the North American study over a median duration of monitoring of 16 weeks, 85 percent of patients who responded continued to meet response criteria, and in the international study over a median duration of 12 weeks, 87 percent of the responders had not relapsed.

Again, we turn to the Kaplan-Meier analysis to better assess the duration of response, and here for the North American study showing the percent of patients who relapsed versus response duration, we see that the Panretin gel patients shown here in yellow have not begun to approach the median even out as far as 400 days, at which time only 24 percent of responders are projected to have relapsed for

those patients on-study. Again, although there were fewer patients in the international study, the results are consistent.

Finally, looking at a Kaplan-Meier analysis for the time to progression for the North American study, showing here the percent of patients who have progressive disease versus the time to progressive disease, we see that the time to progression for Panretin gel shown in yellow is consistently shorter than that for vehicle and was significant with a p-value of 0.018.

Once again, for the international study, although there were fewer patients, the results were entirely consistent and supportive.

Turning then to some other secondary efficacy endpoints, the physician's global and subjective assessments, both of these studies used the same grading scale by the physicians in which a partial response constituted a 50 to 90 percent but less than 100 percent clearing, progressive disease was 25 percent worsening, and as with the ACTG criteria, we required a confirmation over two study visits separated by at least four study weeks.

For the North American study shown on the right are the responses according to the physician's global assessment, with 19 percent-plus for Panretin versus less than 4 percent for vehicle, substantially different for

treatment arms, and although the absolute response rates were less than the ACTG criteria response rates shown on the left, it is particularly noteworthy that the additive difference between treatment arms is maintained.

For the international study, applying the same scale, physicians noted improvement of 50 percent or more in 47 percent of Panretin patients versus 11 percent of vehicle, substantially different between treatment arms, and fully supportive of the more objective ACTG criteria.

Another secondary endpoint was the patients' own self-assessments of their course on-study. For the North American study, because there was no existing validated questionnaire, Ligand took FDA's suggestion and wrote a questionnaire designed to measure the patients' subjective feelings about their treatment on-study. We adapted from the KS module of ACTG 286, with permission of the authors, including Marcia Testa, a questionnaire that was then analyzed according to FDA recommendations and after consultation with Dr. Testa.

The method of analysis was based on mean scores and change scores from baseline and then an application of the two-stage model based on Little's pattern mixture model to assess missing data and a longitudinal analysis to obtain robust results. This analysis consisted of separate analysis for the patients who completed 12 weeks and those

who did not complete 12 weeks and looked at data points at weeks 4, 8, 12, 16, and 20 on the initial blinded therapy. The level of statistical significance was determined by the general linear mixed effects model for longitudinal analysis, considering all data from weeks 4 through 20.

Compliance for this questionnaire was quite high, with 95 percent of patients -- all but 14 -- completing the questionnaire at baseline, and of those patients completing at baseline, 93 percent had at least one post-baseline questionnaire. Of these 249 patients with both pre and post data, 93 percent of questionnaires were completed for those patients who attended clinic visits, and 97 percent of the patient questionnaires were self-administered by the patient.

This slide shows the questions that were administered and consisted of five general status questions: feelings about overall physical, emotional, personal, and job/work, and then four KS-specific questions. As you can see, three of the four KS-specific questions had scores which statistically favored Panretin gel over vehicle, as did the sum of all nine questions.

I would like to note that the one question that favored vehicle, the job/work feeling question, was particularly problematic in the study in that a large number of patients were not occupationally employed and failed to

answer this question as a result. The average completion rate for this question was notably lower than the other questions and was only 37 percent during the initial blinded phase for the 12 week completers.

I would now like to show you line plots for the three of four KS-specific questions and the sum of nine questions which favored Panretin gel, the first question being physical appearance. For the 179 12 week completers, where we look at the mean score versus weeks on study. I would like to point out that in each of these quality of life scores, the amount of data after 12 weeks is small and that for the first data point, between 76 and 91 patients were contributing data, but after week 12, which was the intended study treatment, the number of patients contributing data at week 16 drops off dramatically to only 19 to 21 patients, and the number of patients contributing data at week 20 is only 2 or 3 patients. For this reason, I have shown the curves following week 12 as dotted lines because of the paucity of data after 12 weeks and because of the potential for bias. So for this question, asking the patients about their physical appearance with regard to Panretin gel, it can be seen that for Panretin gel patients in yellow, these patients rated their physical appearance nearly in the range of 4, moderately satisfied, compared to vehicle gel patients who rated themselves on the average

mildly dissatisfied.

For the next question, the change in treated KS lesions, Panretin gel patients rated themselves generally 1, moderately improved, versus vehicle gel patients 0, about the same.

For the question regarding the overall level of satisfaction with regard to study drug, Panretin patients rated themselves generally 1, moderately satisfied, versus vehicle patients rating themselves 0, neutral.

Finally, for the overall sum of nine questions, Panretin patients rated themselves higher than vehicle, substantially different, with a p-value of 0.0002.

This shows, again, all nine questions. I have shown you the line plots for those questions favoring Panretin gel over vehicle for the 12 week completers, and would like to point out that for the 12 week non-completers, what the FDA calls the dropout group, the results were also substantially in favor of Panretin gel for these same questions, including the sum of all nine questions.

Turning then to the international study, where there was low quality of life scores but patients applied the same subjective grading scale as did physicians, we see on the right that physicians rated themselves at least 50 percent improved 47 percent of the time on Panretin gel versus 11 percent on vehicle, substantially different

between treatment arms and virtually mirroring the more objective ACTG response criteria on the left.

A comment about individual lesion responses. While the primary endpoint was based on the patient rather than the lesion as the unit of analysis, physicians and patients alike are likely to be interested in the likelihood of individual lesions responding, and in these studies we treated more than 2,200 index lesions, as well as a great many other non-index lesions. Twenty-eight percent of these index lesions met at least a 50 percent response, and 6.4 percent of all lesions completely resolved. Two-thirds of patients had at least one lesion partially respond, and 18 percent of patients had at least one lesion completely resolve.

At this point, I would like to make a few very important comments about the photographs. While the ACTG cited the importance of photographs in the evaluation of KS, at the same time, in their 1989 publication, they pointed out the limitations of attempting to use photographs for the determination of response, stating that photographs may fail to fully capture the character of lesions -- that is, nodularity and color. There should be no uncertainty that photographs in all of these studies were prospectively defined in the protocols as only supporting data. They were neither primary nor secondary efficacy endpoints, and they

were included largely at the request of the FDA.

Although it was known to Ligand from the phase 1-2 studies that consistent high quality photographs were difficult to attain, Ligand undertook efforts to standardize photographs to the extent possible in the North American study. However, even with diligent efforts, photographs are only as good as the level of standardization and the quality of skill of the photographer at the study centers. As a two-dimensional medium, they cannot accurately capture lesion height, and they are subject to various artifact. It may be harder in photographs than at the bedside to distinguish between erythema surrounding the KS lesion from the lesion pigmentation itself. Finally, with the patient as the unit of analysis, various lesion photographs do not readily provide an easy integrated evaluation of all indexed lesions over all visits.

For these reasons, photographs remain inferior to hands-on direct evaluation by investigators, and that response and patient benefit cannot be reliably determined in these studies from photographs alone.

At this point, I would like to make a few comments and show some data regarding the medical and statistical review by the FDA of this NDA. Most importantly, I would like to emphasize that for the protocol defined, primary efficacy endpoint based on objective tumor response

assessments, the FDA has concurred with the Ligand-designated Panretin gel responders in 98 percent of patients in the North American study and 93 percent of patients in the international study. I should add that we are prepared to provide data why the two patients that were excluded should indeed be considered ACTG responders.

I will be discussing two important aspects of the FDA review, namely the FDA's beneficial response analysis and FDA issues with regard to the interim analysis of the phase 3 study, the international study.

The FDA introduced a new analysis during their review of this NDA, analysis termed beneficial response. I should say that, first, while we appreciate the tremendous work undertaken by FDA to review individually all of the indexed lesion photographs, we do have serious concerns about the appropriateness of this type of analysis and how they would be positioned by the FDA. FDA found beneficial response in about half of the responders who had been determined to meet the primary endpoint according to ACTG, and Ligand disagrees with the beneficial analysis and believes that the ACTG responders did in fact experience benefit.

So, for a number of reasons, which I will now review, we believe that the analysis of beneficial response is not an appropriate analysis. For example, this analysis

was based on primarily supportive-only data -- that is, photographs. Photographs were not a primary efficacy endpoint. They were not a secondary efficacy endpoint. This was a retrospective ad hoc analysis that was not specified in the protocol.

It remains unspecified as to the algorithm used for the determination of beneficial response and appears to discount secondary efficacy endpoint data from both patients' and investigators' assessments. I would also like to point out that some of the ACTG responders appear to have been determined to lack benefit by the FDA not because the photographs might be interpreted as possibly refuting response, but rather because either photographs were not taken or they were of such poor quality as to be of no use. In short, these patients appear to have been defaulted to a non-response category by the FDA. Finally, as a reminder of the many limitations in attempting to score response by photos, the FDA's Medical Review makes the point that it is difficult to score tumor response using photographs alone.

Perhaps most importantly, the study patients' own assessments appear to disagree with the FDA's beneficial response. These self-assessments by the patients who are perhaps probably best-suited to evaluate their own degree of benefit should not be discounted in favor of an unblinded third-party review of photographs. Patients are able to

consider not only the physical appearance of treated lesions, as may or may not be apparent in the photos, but other aspects of benefit.

I will now show data from both phase 3 studies for the group of ACTG responding patients who were determined to lack beneficial response by the FDA, both using the quality of life scores in the North American study and the patient's subjective assessments in the international study. This is a quality of life questionnaire for the overall level of satisfaction with study drug for the 24 ACTG responders who were determined by the FDA to lack beneficial response. The grading of this score was such that in the lightly shaded area patients were rating themselves as either moderately satisfied or very satisfied. There is a plot on this table for each of the -- a line plot for each of the individual 24 patients, and as you can see, all but a few patients -- that is the majority of patients -- rated themselves in the range of very satisfied to moderately satisfied and that this benefit was sustained for data that we have patients going out well beyond the initial blinded phase.

Taking another question from the quality of life -- that is, patient's assessment of the change in their treated KS lesions -- once again, an individual line plot for each of these 24 patients. We see that the majority of patients for most time points rated themselves in the range

of 4, moderately improved, to 5, much improved.

In the international study where we did the comparative analysis and we look at the eight ACTG responders who are determined by FDA to lack beneficial response, this graph looking at the patient's subjective assessment where the lightly shaded box represents a 50 percent to 100 percent improvement, we see that all but one of the patients rated themselves at least 50 percent improved. In fact, three patients shown here rated themselves 90 percent improved.

Data from the physicians' assessments in both phase 3 studies also appears to disagree with conclusions according to the beneficial response analysis. KS-treating physicians have the advantage of direct, hands-on evaluation of patients and their lesions, avoiding many of the problems inherent in attempting to use photographs to score response, and I will show you data from both studies, again, this time using the physician's global subjective assessments.

Again, for the 24 ACTG responders in the North American study determined to lack beneficial response according to FDA, here looking at the physician's global assessment, the shaded area again being a 50 to 100 percent improvement, the physician's scoring of improvement of these patients shown in the lightly shaded area appears to contradict the assessment of beneficial response according

to FDA. Also noteworthy, while the FDA appears to make an issue of the similar response rates in the North American study for physician's global assessment and their response rate for beneficial response, I think it is evident from this plot that these are not the same subset of patients but actually are distinct patient population subsets.

Lastly, turning to the international study, looking at the physician's subjective assessment for the eight patients that were ACTG criteria responders but lacked clinical benefit, lacked beneficial response according to the FDA, we see that all but one patient have been scored by their physicians to have a 50 percent or better improvement. Three patients were scored in the 90 percent improved range, and one patient was scored as 100 percent improvement with complete clearing.

So then, with the preponderance of the data clearly appearing to contradict the beneficial response assessment, what can we learn from photographs? Our review shows that many lesions nevertheless improved in these patients who were determined to lack beneficial response. One factor that may have influenced the FDA's inability to more clearly distinguish response from the photographs, in addition to limitations I have already stated, is the occurrence of irritation temporarily at the lesion which may mask for a period of time the full benefit, and I would like

to run through quickly just a few photographs.

This is a patient in the North American study, an ACTG responder found to lack benefit by FDA, a lesion on the thigh, at baseline and then at week 27, showing considerable reduction in the intensity of pigmentation, some reduction in size, and notable central clearing of the lesion.

A lesion from a different patient in the same -- also an ACTG responder who lacked benefit according to the FDA -- a lesion on the posterior thigh at baseline and at week 4.

This series of photographs for yet a different patient shows a lesion on the leg at baseline and then at week 58. This was the last lesion that was available to FDA, submitted with the NDA, showing some very typical retinoid irritation, a little bit of erythema and scaling over the lesion. If we look at a lesion that was obtained at a date which made it impossible for us to submit the photograph with the NDA, we see that the lesion is completely resolved.

And for yet a fourth patient, similar scenario where we are looking at the lesion at baseline -- this is a lesion on the abdomen -- and then a lesion at approximately week 13, which was the last photograph able to be submitted with the NDA, and then a later photograph showing complete clearing of the lesion.

So to summarize our perspective on the beneficial response analysis, I would like to reiterate this analysis was not appropriate. The endpoint was not specified in the protocol. Both the patients' self-assessments and the physician assessments appear to disagree. In patients found to lack beneficial response by the FDA, many of the lesions did improve. I would like to emphasize that benefit does involve more than the photographic appearance of the lesions.

Turning now to issues regarding the interim analysis of the international study, the FDA's statistical review raised the following issues: imbalanced patient assignment, the number of patients in the interim analysis, the appropriate statistical test and stopping criteria, a response rate that was lowered slightly by the admission of one patient, and the statement that secondary endpoints may not be supportive. These together appear to cause the FDA to challenge the robustness of the interim results.

As I have stated earlier, these issues had been previously identified by Ligand and communicated to FDA both at the pre-NDA meeting and in the formal statistical plan after the study was stopped but well in advance of filing of the NDA.

The blinded randomization in the international study resulted in 36 patients assigned to Panretin and 46 to

vehicle. This difference resulted from a tendency in the randomization blocks of four to assign more patients to vehicle at those centers enrolling patients in the 82-patient interim analysis data set, with the majority of those centers -- 10 of 17, to be exact -- enrolling fewer than four patients. The Chi-square test, with a target of 0.00025 for the interim analysis, is the preferred statistical test. The O'Brien and Fleming guideline was properly used for the 82-patient cohort, and the application of the appropriate statistical test met conditions of the protocol-specified Chi-square test, where if we look at the Ligand-identified 15 patient ACTG responders, a p-value of 0.00015, meeting the target, or alternatively if we used the FDA's defined 14 ACTG responders and apply the Lan-Zucker modified boundary rule as specified by FDA, the p-value of 0.00033 also meets that target using the Lan-Zucker.

The secondary endpoints, I hope as you have seen, from the Kaplan-Meier are quite supportive of the primary efficacy endpoint according to ACTG criteria.

Ligand sought the help of a third-party independent biostatistician to address these issues and retained Dr. Thomas Fleming. Dr. Fleming reviewed the conduct and results of the interim analysis and came to the following conclusions: the interim analysis of the 36 versus 46 patient treatment groups was consistent with the

protocol; the boundary criteria were met in this interim analysis; and the interim analysis findings were reinforced by the 134-patient final data set analysis.

At this point, I would like to resume my presentation of the study data with a summary of the trial results by re-focusing on the protocol-specified primary efficacy endpoint. In each of the clinical trials shown here, the response rate for patients on Panretin gel exceeded 25 percent. In each of these studies, the response rate difference between Panretin and control was highly statistically significant, and in each of these studies, the difference in response rates between Panretin and vehicle was more than 15 additive percentage points.

Taken together then, these studies comprise the largest double-blind well-controlled clinical trials of a topical agent in AIDS-related KS. The superiority of Panretin gel over control was consistently demonstrated in all studies, with response determined by the standardized widely accepted ACTG criteria, and corroborated by all secondary efficacy endpoints, including the patients' own self-assessments.

Panretin gel produces objective responses in KS lesions and results in disappearance of some lesions. It reduces the rate of progression and increases the time to progression of lesions. The responses are durable, and

quality of life was improved according to the patients' own self-assessments. The gel was found to be convenient, easily applied, and allowed for patient-controlled application.

The superiority of Panretin gel over control was maintained after consideration of a wide array of variables. Responses to gel were found to be not attributable to any possible effects of concurrent antiretroviral therapy, and responses were not dependent on immunologic status, with responses seen in patients with CD4 counts as low as 0 to 50.

The responses to Panretin were uniformly observed, not only in treatment-naïve patients, but patients with one or more prior systemic or topical local therapies and even in some patients who were refractory to systemic and/or prior topical or local therapy.

So in conclusion, Panretin gel 0.1 percent, applied topically, at a frequency of two to four times a day, is effective as first-line therapy for cutaneous lesions in patients with AIDS-related KS.

I thank you for your attention. You will now hear from Dr. Reich regarding safety findings from these studies.

Agenda Item: Safety Data of Panretin Gel: Steven D. Reich

DR. REICH: Thank you.

This morning I will be describing the safety profile of Panretin gel. To give you the conclusion first, the safety database clearly shows that Panretin gel administered for first-line topical treatment of cutaneous lesions in patients with AIDS-related KS was generally well-tolerated and safe. The safety database consists of the phase 1-2 program conducted at nine U.S. centers with 115 patients enrolled, the North American phase 3 study with 268 patients enrolled, and the international phase 3 study of the first 82 patients enrolled. Of the 465 patients with AIDS-related KS enrolled in these trials, 385 patients were treated with Panretin gel. The longest duration of treatment in this database was up to 96 weeks.

It is important to understand the proposed dose regimen as one considers the safety. We believe that Panretin gel should be initially applied 2 to 3 times to cutaneous KS lesions. The application frequency can be increased to 4 times a day according to individual lesion tolerance. If application site toxicity occurs, the application frequency can be reduced. Should there be severe irritation, the application of the drug can be temporarily discontinued for a few days until such symptoms

subside.

There is very little systemic exposure of this drug. During the phase 1-2 clinical trial program, using an assay with a level of detection of 2.5 nanograms per milliliter, there were no plasma concentrations detected. Using an assay with 10-fold sensitivity, we found that those patients who were tested had 9-cis-retinoic acid levels that were comparable to those in untreated patients.

This limited exposure is reflected in the number of deaths and serious adverse events that occurred during the studies. There was no excess number of deaths, with five deaths in the Panretin group and six in the vehicle gel group, and there was no death reported to be related to Panretin gel. There was no excessive serious adverse events. The only two serious adverse events related to Panretin gel occurred sequentially in the same patient and consisted of a cellulitis and a positive blood culture in a patient who scratched a pruritic lesion.

For the 161 patients who received Panretin gel at a concentration of 0.1 percent for more than 16 weeks, Panretin gel was generally well-tolerated. For the phase 3 studies, withdrawal to adverse events was uncommon, with only 7 percent of the patients who received Panretin gel withdrawing, primarily for local rash and/or pain.

Adverse events associated with Panretin gel were

principally confined to the cutaneous application site, were nearly exclusively mild to moderate, and could be managed by reduction in application frequency or by interruption or discontinuation of treatment. It is clear that Panretin gel can be irritating to the skin, and the most common related adverse events include rash, pain, and pruritis at the application site.

Ligand uses COSTART 5 as its coding dictionary to categorize events, and this particular dictionary is not optimized for topical treatments. Several investigative terms code to rash, including such descriptive terms as redness and erythema, as well as terms such as scaling, irritation, rash, and dermatitis, which suggest symptoms. The category of skin disorder consisted of a whole variety of terms. It is important to note that such investigator terms as flaking and peeling at the local application site did code to exfoliative dermatitis, and so this terms reflects the local, not systemic, reaction.

As we look at the application site adverse events with at least 5 percent incidence in the blinded phases for both North American and international studies, we see that rash, pain, and pruritis are the most common effects.

The difference in the incidence of rash, pain, pruritis and the other events in the two studies deserves comment. For the adverse events listed on the previous

slide, the international study still had a lower overall, which includes both application site and systemic events, incidence. Using overall incidence, the adverse event profiles are closer together, but there still appears to be a difference.

There are inherent risks of comparing two independently run studies for adverse events. The difference in dosing -- namely twice a day in the international study and three to four times a day in the North American study -- may be one reason for this difference, but there are other possible explanations. The amount of gel applied to lesions may have been different in the two studies. Patients in the North American study may have had a greater number of lesions treated; so more were at risk of developing a toxicity. Reporting threshold at the sites in Europe and Australia compared to North American sites and differences in terminology probably played a role. For example, burning codes to pain, but stinging codes to paresthesia. There may be other confounding variables, as well.

As we look at the most frequent related events, we see again that mild to moderate rash, pain, skin disorder, and pruritis are the most common. The number of severe events is actually quite limited, with about 10 percent of the patients having a severe rash and only about 4 percent

of the patients having severe pain.

Rash is usually described as erythema or scaling at the application site. It may be seen as early as day 1, but about half the patients who develop rash do so by week 2. The rash may last as long as the drug is applied and, according to investigators, resolves 2 weeks after drug discontinuation. The median time to develop severe rash was 22 days for those 36 patients with severe rash. Most are treated with dose adjustment or interruption. Median time to resolution of the rash was at least 102 days.

Pain occurred primarily at the site of application. It was often described as occurring at the time of gel administration. For the 14 patients with severe pain, the median onset occurred at 8 weeks and median time to resolution was at least 9 days. Most patients were treated with dose-adjustment or treatment interruption.

Some patients described stinging or tingling at the time of gel application, and these events were coded to the COSTART dictionary term of paresthesia.

Analysis of the database resulted in some other findings pertaining to safety. Increased exposure based on the number of days at a particular frequency of application of Panretin gel was associated with only a slight increase in incidence of adverse events, with most at the cutaneous application site. There is no data to suggest unusual

adverse events based on anatomic location of the lesions. There were no photosensitivity reactions related to Panretin gel, and once the drug was discontinued there were no adverse withdrawal effects that were attributed to Panretin gel.

There were no subpopulations that had an increased incidence of adverse events. As we reviewed the clinical data in terms of clinical laboratory measurements, drug-drug interactions, and emerging opportunistic infections, there appeared to be no changes consistent with a minimal systemic exposure.

In conclusion, Panretin gel has an acceptable safety profile, which includes the near absence of drug-related systemic toxicities. Panretin gel presents a very favorable risk-benefit ratio for the topical treatment of cutaneous lesions in patients with AIDS-related KS.

With that, I would like to now introduce Dr. Barbara Melosky, an investigator on the North American study, who will discuss patient benefits.

Agenda Item: A Clinical Investigator's Perspective: Barbara Melosky

DR. MELOSKY: Good morning. My name is Barbara Melosky. I am a medical oncologist from Canada. I work at the Cancer Agency in Vancouver in British Columbia. As a medical oncologist, I treat breast cancer, lung cancer, and

Kaposi's sarcoma, and as head of the Kaposi's Sarcoma Tumour Group at that center. We are a member of the NCI-Canada and do many trials with them, and I am a member of the AIDS Care Team at the Western HIV Hospital, St. Paul's Hospital, in Vancouver, Canada.

We participated in the North American trial, had 28 applicants, and are currently still treating 5. All patients continued to be on the follow-up.

As a medical oncologist, I see Kaposi's sarcoma really being within two groups. Those are the symptomatic visceral disease, requiring systemic chemotherapy, which I apply, and those require the local treatments with mucocutaneous disease. Just a note: at the Cancer Agency where I work, it is a multidisciplinary system. So we have easy access to radiation oncologists, dermatologists that do the intralesional treatments, dentists who do the mucal mouth treatments, and as well, many cryotherapies done by the family doctors. It is to note that the Panretin gel has an advantage over these therapies. As reviewed by Dr. Miles, the cryotherapy, intralesional chemotherapy, and radiation have some morbidities attached to them.

There are side effects of this gel. With our experience with the 28 patients, we did see irritation at the application site. This was common within the first 8 weeks of application. It was not painful, nor severe. It

was well-tolerated by the patients. It resolved within 6 to 8 weeks with a dose adjustment.

The clinical benefit was actually clear. These lesions became flatter. They became lighter, and they became smaller. Some lesions completely resolved, and even when lesions did not completely resolve, the partial response was excellent, and patients were extremely satisfied.

Finally, just to show you a single patient from one of our 28, this is an eyebrow lesion, and you can see by week 21.9, the lesion is settling nicely, and by week 41.9 has almost completely resolved.

I would like to invite Dr. Neil Bodsworth to speak next.

Agenda Item: A Clinical Investigator's Perspective: Neil J. Bodsworth

DR. BODSWORTH: Thank you, Dr. Melosky.

I work at the Taylor Square Clinic in central Sydney. This is Australia's busiest HIV clinic, and we currently look after some 2,200 HIV patients, of whom 36 enrolled into the international phase 3 study.

Today I would like to briefly describe the experience of two of our patients who received some benefit from this drug for the cutaneous KS. In the first case, KS lesions first developed during 1995 and progressed

throughout 1996 despite radiotherapy, protease therapy, and some herbal remedies. Thirteen lesions were treated with the Accugel(?), including seven indicated lesions, and each of the indicated lesions resolved after 8 weeks of therapy and remained gone at week 12 and through almost 2 years of follow-up.

These are four of the indicated lesions that appeared that were treated in this man's groin. At 12 weeks, the lesions, as you can see, had disappeared, although there remains a little skin irritation, and there was a very good result here on the right in the long-term. This picture was taken just last week.

This patient received a great psychological boost from his KS disappearing, which had engendered his first optimism about the future, as well as markedly improving his social life.

The second case I would like to show you had KS again for a year before enrolling, and during that time had received radiotherapy as well as intralesional phenblestin(?). He was randomized to receive the vehicle gel, and there was no change during the 12 weeks of the blinded phase of the study, despite a more than 50 percent increase in his CD4 count. However, after 36 weeks of open-label therapy, all his index lesions and all his other pretreated lesions had resolved.

This is the appearance of one of the lesions, an abdominal lesion, at baseline and after 12 weeks on placebo, and a very, very good result after 36 weeks of active gel on the right.

This man works in an AIDS welfare agency with the stigmata of KS well-known. So he was very pleased that all his lesions had resolved, including all his previously treated lesions. He also commented on the near absence of toxicity compared to his earlier therapies. In particular, there was a far better cosmetic result on the face where early radiotherapy of other lesions had left noticeable divots in the skin.

So we found the gel to be effective in resolving many flat and nodular KS lesions, including longstanding lesions, pretreated lesions, and lesions at various anatomic sites. It was also effective in patients with advanced HIV infection and low CD4 counts, a group who are often less tolerant of other more invasive therapies.

We also observed that it could take up to over a year of gel application to achieve maximal results. Residual markings are minimal in the long-term, and to date we have seen no evidence of any relapse in responding lesions at our clinic.

Dr. Miles and the patient testimonials have well aired the potential advantages of an effective topical cream

for the treatment of this disease. Suffice it to say I would certainly prescribe this compound for cutaneous Kaposi's sarcoma if it were to become available.

Thanks very much, and I believe we have Dr. Holden now to summarize.

Agenda Item: Summary and Questions: Howard T. Holden

DR. HOLDEN: In summary, I would just like to say that through the analysis of the two randomized placebo-controlled phase 3 trials, the North America and the international study, overall, in terms of the primary efficacy endpoint, Panretin gel was favored over vehicle, and for all of the secondary endpoints that we looked at, time to response, duration of response, time progression, physicians' and patients' assessment of Panretin gel over vehicle gel for the various endpoints that were designed into the study.

We would contend that Panretin gel is safe and effective for a first-line topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma.

We would be very pleased to entertain any questions at this time.

DR. DUTCHER: Thank you.

Are there questions for the sponsor from the committee?

Dr. Abrams?

DR. ABRAMS: I am curious as to any information you might have on the adherence of patients to their regimens, particularly in the North American TID and QID applications, especially -- my concern is that this is a cosmetic treatment, and if I were a patient with a KS lesion, I would be hard pressed to continue to apply something three or four times a day for 50 weeks if I were not yet seeing some dramatic response. What motivates patients to continue to apply this agent three times a day when there is not a very rapid response occurring? So did you do any assessment of adherence?

DR. HOLDEN: Yes, we did. There was some information in the case report forms that dealt with this, and Dr. Yocum will respond to the question.

DR. YOCUM: Thank you. I would like to respond to the question and also to the comment about cosmetic treatment. I think that cosmetic is probably an inadequate term to describe the range of benefits accrued to patients on Panretin gel. These studies have demonstrated objective tumor responses and some complete lesion resolution. We have seen from Dr. Miles at least one biopsy that showed complete histologic resolution of a treated lesion, and the beneficial effects, which include not only objective tumor responses, we believe extend well beyond cosmesis. We have

heard some of the patients today speak to their own experiences and how it resulted in substantial -- in some cases life-altering improvements -- in their social and psychological well-being.

DR. ABRAMS: I mean cosmetic to involving visceral organs and having any impact on overall morbidity and mortality.

DR. YOCUM: Thank you for that clarification.

May I have that slide, please, 506?

As you note in the North American study, the protocol-defined treatment was initial treatment with TID and then escalating to QID after two weeks as tolerated. This slide shows the maximal exposure attained for patients in that study. While there were a few protocol deviations of patients who actually started at BID in violation of the protocol, 70 percent of the patients were able to attain QID application, with a majority of those patients who were able to remain at that concentration.

DR. ABRAMS: So you knew that patients were actually applying it four times a day? I mean, there was some --

DR. YOCUM: The case report form was designed actually on an individual lesion basis so that when the patient returned to the clinic visit, there was a box on the case report form querying the patient or the investigator to

enter the actual applied frequency of application -- not necessarily the prescribed treatment, but the actual treatment that was being utilized by the patient.

DR. ABRAMS: So there was no dose response, but there appears to be an increased toxicity at TID and QID, and there was a better overall response in the international study where there was a BID dose. So how do we rationalize the TID?

DR. YOCUM: Let me first address your statement about the safety dose response, if I can have just a moment here. If I could please have -- I do not seem to be able to find the slide, but as noted in the background briefing document under the section regarding the recommended dose regimen, while some of the adverse events appeared to have perhaps a slight although maybe not substantial increase in toxicity in terms of the adverse events of rash and pain, for many other events the incidence of events across the various application frequencies was variable and not consistent. So I think that looking at the data from the integrated summary of safety, it is really not clear -- or actually the data would speak against a consistent dose effect in terms of the majority of adverse events that were recorded.

DR. ABRAMS: I am also interested in the first-line indication. In the North American study, the number of

patients who had had prior anti-KS therapy was 65 percent. So that means one-third out of 134 patients were receiving this as their first-line therapy. And you did show us a graph that shows that they had an acceptable response, but you also showed that patients with prior systemic and people who were refractory to prior therapy also have beneficial responses. So what is the rationale here for suggesting that it should be first-line?

DR. YOCUM: Well, by the use of first-line in the draft proposed labeling, we did not mean this to be restrictive to patients that had not been prior treated, but that it would be appropriate for treatment-naïve patients as shown in the clinical studies, but that it would also be appropriate for patients that had had prior systemic or topical local therapy. We have heard some anecdotal stories from patients here that have had individual lesions that have received prior therapy and either enjoyed further improvement or in fact responded only after the Panretin gel treatment.

DR. ABRAMS: So the actual number of people who received Panretin gel as first-line therapy is what?

DR. YOCUM: Could I have slide 128, please? This was the slide that you alluded to that I showed in my presentation where we looked at the response versus prior anti-KS therapy for both of the phase 3 studies, and you

will see the North American study in green and the international study in lavender. I think it is number 128.

So these are the responses to Panretin gel. So we saw 21 out of 47 patients in the North American study and 10 out of 43 patients in the international study in the treatment-naïve group. These are patients that had neither prior systemic nor prior topical local therapy.

DR. ABRAMS: On slide 112, where we looked at the baseline extent of disease, why don't we have any information on the median duration of KS or the patients with greater than 50 lesions from the international cohort? Why is that missing?

DR. YOCUM: The case report forms did not collect any of that data in the international study.

DR. ABRAMS: Finally, the issue about photographs is an interesting issue. Dr. Miles showed us in the patient who had the histologic complete response a picture of a lesion that he called was completely resolved when the lesion was still there, and then we just saw from Dr. Bosworth a lesion at week 12 in a patient receiving vehicle that he called unchanged that to me looked like a nice partial response. So I agree that there is some difficulty here in using the photographs completely, and I do not think that Dr. Miles meant that that was a complete resolution, although it was perhaps histologically without evidence of

spindle cells. There certainly was a lesion that was still there that was visible to the eye.

DR. MILES: I agree with you regards to the evaluation and use of photographs, and that is a perfect example. That lesion actually was gone, and I could tell from having been the clinician who did the punch biopsy that that was residual effect from the drug. So when we did the biopsy, we were expecting to see irritation and we were looking to see what the mechanism of response was. In fact, what we saw was complete resolution and no irritation at all.

DR. ABRAMS: But clinically we would not call that a complete response.

DR. MILES: Using the photographs alone, you would not call that a clinical response. That is correct. And the patient was not scored a clinical complete response. He was actually scored as a partial response.

DR. DUTCHER: Dr. Krook?

DR. KROOK: Generally, a comment first is that if I look at the efficiency in the endpoint results, I do note that 18 percent at least were judged as a response with the gel only, and perhaps -- I am not one who sees Kaposi's sarcoma very often, living in the cold country, but certainly the vehicle must have some effect or else some of these things are spontaneously resolving. I would be

interested in the number of patients who perhaps dropped out in the 12 weeks just secondary to the side effects. I do not know whether you have that or not, but obviously here there is a 12 week study period, and a lot of data is there, and some of them continued on, and the number which continued on with either vehicle -- as I look at the way the study was set up. But certainly, there appears to be -- I mean, this committee has looked at responses of 12 and 4 percent, and we have made judgments on that, and here we have a placebo control which does it, an 18 by your judgment.

DR. HOLDEN: Dr. Yocum?

DR. YOCUM: Perhaps we could go back to a slide in my presentation, number 231. With regard to the vehicle response rates in these studies, I would like to point out that the response rate was nearly 18 percent in the North American study, but if we look across the other studies, the response rate was just under 7 percent in the international study, and we had a response rate on the control untreated lesions of 11 percent in the phase 1-2 studies. We certainly expect to see some degree of response to placebo in any clinical trials, and I do not think I need to remind the committee that AIDS KS is a very complex interactive disease state.

The blinded randomized trial design was in fact

chosen to control for placebo effect, and the studies were not designed to evaluate a vehicle response rate, per se, but in fact were designed to evaluate the treatment effect, and when you compare the response to Panretin gel over vehicle, as I have shown you here, the results were highly statistically significant for each of the studies we have conducted.

DR. KROOK: Another question which follows on that, in the North American study the time of the duration was 12 weeks. Did those on vehicle control, were they all given the chance to cross over to Panretin at 12 weeks, and how many did? I mean, now they have had 12 weeks of applying TID or QID and were now given -- and I guess, was the code broken at that point -- and were given that opportunity to be on the open-label?

DR. YOCUM: The randomization blind was not broken when the patient switched to the open-label therapy. None of the blinds were broken until the very last patient had completed, the last of the 268 patients had either withdrawn or completed from the initial blinded phase, and then the randomization was coded for all of the patients entered in the study at that time.

DR. KROOK: So there were some patients who continued on vehicle control longer than 12 weeks?

DR. YOCUM: Yes, let me just answer first -- you

asked me how many vehicle patients had been switched to open-label, and the number was 85 out of 134 patients.

We speak in simplistic terms of a 12-week initial blinded phase, where in fact the protocol was written such that if the patient had onset of either response or onset of progressive disease at week 12, the investigator could hold that patient over on the initial blinded therapy for another four more weeks to see whether that was confirmed, rather than switching that patient over to open-label at that time. So most of the patients were treated at 12 weeks, but some were treated weeks longer than 12. That was true for both vehicle and Panretin groups.

DR. ABRAMS: But nobody applied vehicle for 52 weeks, for example?

DR. YOCUM: I do not believe the vehicle was applied for that long. I cannot tell you exactly what the duration is, but we could look that up if you would like.

[Pause.]

I am told that the longest duration of vehicle treatment was 24 weeks.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: I have three questions, or three related questions. The first question is the choice of topical therapy versus systemic therapy. Did it have to do with the hyperlipidemia expected with the heart therapy as

well as the 9-cis-retinoic acid, and the related pharmacologic question: what is known about the penetration of the topical 9-cis-retinoic acid into the cells of the Kaposi's lesions? That is question number one.

DR. YOCUM: I would like to address the penetration/skin absorption issue first.

DR. MARGOLIN: And the choice of topical versus systemic.

DR. YOCUM: Perhaps we could have Dr. Loewen, our pharmacokineticist address that question.

DR. LOEWEN: Do you have the absorption slide, please? Number 11, please.

We actually, in direct reference to the question involving penetration of the drug into the KS lesions, we have not actually evaluated concentrations in the KS lesions. We do, however, have data from two studies in which we evaluated the ability of the drug to penetrate into and through the epidermis and dermal layers. A study with human cadaver skin indicated that a 9-cis alcoholic gel was in fact capable of penetrating into and through the epidermis and dermis, and also a published study by Dual(?), et al, indicated that application of a 9-cis-retinoic acid alcoholic gel was capable of penetrating into the dermis.

DR. MARGOLIN: Thank you. The second question, which is somewhat related, is I believe I saw -- but I do

not remember and you did not mention -- data on the use of topical isotretinoin or 13-cis-retinoic acid in the same setting. Are there such data, since that is an approved drug.

DR. YOCUM: We have not collected, ourselves, data on the application of other retinoids in clinical trials, but to address your first question regarding the oral administration versus topical administration, we have conducted two phase 2 trials of the oral formulation of allitretinoin Panretin capsules in patients with AIDS-related KS. More accurately, one of those studies was directly sponsored by Ligand. The other was sponsored by the AIDS Malignancy Consortium under sponsorship of the NCI. Those two studies enrolled a combined total of 123 patients and showed response rates according to ACTG criteria in a range of 36 percent or so. So we are in fact looking at clinical trial data for both oral and the topical formulations.

DR. MARGOLIN: And my last question has to do with the patient, the quality of life information and patient satisfaction surveys that you showed. The data are rather compelling, if those p-values are really true, which is somewhat hard to believe, but although this was placebo controlled, and I interpret that as meaning really a control for the effect of heart or whatever therapies there are for

systemic AIDS -- it is hard to imagine that most of these patients were not aware of what treatment arm they were on in view of the high incidence of irritation and rashes. Patients, obviously, who know they are on the active therapy may be more likely to be satisfied with the fact that they are on active therapy, regardless of the clinical response to the therapy. So I just wondered about your comments on that.

DR. YOCUM: I am going to see if I can find a slide that will help me address that. Perhaps we could see if we can cue up number 712 and 713.

You have seen the profiles for the adverse event incidence in the two phase 3 studies, and for the most prevalent adverse event of rash, 70-some percent of patients experienced that, and what that means, of course, is that for those patients, for those 70-some patients, they had rash at at least one of the treated lesions. It does not mean they had rash at every one. They might have been treating multiple lesions but had rash only in one, or more specifically, an irritant effect which mapped to the COSTART term of rash.

So in answer to your question, if we look at the for the adverse event of COSTART term rash, 24 percent of patients in the North American study and 64 percent in the international study had no event of rash in any of their

treated lesions. Conversely, the vehicle treated patients having at least one adverse event of rash, 18 percent of patients in North America and 11 percent in the international.

If I could have the next slide, the comparable analogous information for pain shows that 63 percent of patients in North America and 92 percent in the international had no event of pain -- that is, discomfort -- with application of their treated lesions, index or non-index, and the vehicle patients had at least one event of pain, 13 to 9 percent. So I think there is enough crossover here to confound patients' own assessment of whether they might be receiving Panretin gel or vehicle so as to be not a major issue.

DR. MARGOLIN: But I think you have to be careful with that, because the North American study had more overall applications of drug, and that was the one that had the more formal patient questionnaires than that which was done in the international study, which was a fixed BID dosing schedule.

DR. YOCUM: That is correct.

DR. DUTCHER: Mr. Marco?

MR. MARCO: I have a few comments and then some questions, and I will try to not take too much time.

I think my first comment is, in regard to Dr.

Bodsworth's slide, I take issue with one of his points where he says even useful in patients with advanced HIV and low CD4 counts, less tolerant of chemo or radiation. I really do not think that is true, and I think that is a concept that we have done away with. If we remember to our last NDA or at least to taxol, the median CD4 count of those patients was 17, and it was a very large response rate. So the fact that patients with low CD4 counts cannot tolerate chemo is not true, especially now with GCSF.

Secondly, this is the first study to be conducted in the era of protease inhibitors, and a majority of the patients were on triple therapy. Now, I think something is happening there. I mean, obviously this high placebo rate that has been discussed has to do with the protease inhibitors. Even though the data is still significant, you know, when you exclude for that, let's remember that the median CD4 count in this study, for at least the first one, is 150. Patients usually do not present with KS at 150. For the past 5 years, it has usually been under 100. So obviously they have some enhancement of their immune system. So new lesions may not be appearing if they are not going away.

Then I will get to my questions. The first question is let's talk about refractory to prior KS therapy. Do you have a slide of what these patients were on? Were

they on DOXIL donazome(?) that are approved, or were they on single agent leomycin(?) or BP-16(?)?

DR. YOCUM: Yes, I do have a slide. I can show you that information. This would be slide 710, please.

What I am going to show you are the prior systemic agents for those patients who met the ACTG response criteria for the study, with each of the three studies shown individually. I will not read these to you.

MR. MARCO: Interferon monotherapy?

DR. YOCUM: Yes, the interferon would have been monotherapy. I was kind of anticipating your next question. I think the cytotoxic agents might have been monotherapy. There may have been a combination of leoblencrystin(?), but I think this is primarily monotherapy.

MR. MARCO: Okay, I mean, interferon monotherapy is not recommended in patients under 200 CD4 counts. Single agent leo or phenblastin(?) isn't often used alone. So, I mean, the DOXIL patient that responded, I think, is impressive.

Thalidomide is experimental, as the other therapies are, below DOXIL.

DR. YOCUM: I do not have information to tell you whether the patients with interferon had the labeled required number of CD4 counts or not.

MR. MARCO: Also, for the quality of life

questionnaires, can you tell me what the response rate was? How many filled out fully for all the weeks the quality of life questionnaire versus those that did not?

DR. YOCUM: Let me start with a return to one of my presentation slides regarding the compliance, number 144. I realize I went through this a little quickly, so I will walk through it slower.

In the North American study, with 268 patients randomized total, 14 of those 268 patients did not complete a baseline questionnaire. So we could not compare anything back at the baseline. That left 254 patients. Of those 254 patients who completed the baseline, 5 failed to complete any post-baseline questionnaire. That left me with 249 patients who had a baseline and at least one post-baseline questionnaire. This 93 percent is contingent upon the patient being there at the clinic visit. If they came into the clinic and therefore they had the questionnaire as part of that every four week evaluation, we had a questionnaire that was completed in 93 percent of the time.

Now as patients maybe failed to appear for clinic visits or withdrew from the study, that number is going to go down.

MR. MARCO: Okay, so you have at least a pre and then one post.

DR. YOCUM: In 93 percent, yes.

MR. MARCO: Okay. I guess my last question is what is the mechanism of action for this drug. I mean, it was great to see Steve's slide, and I respect Steve Miles for actually doing a biopsy and looking at seeing if there was a complete response histologically, but what about biopsies and looking at responses? Does this drug lower IL-6 levels? What is going on?

DR. YOCUM: Let me answer your question about biopsies first. While each study was required to have a pre-study biopsy in order to confirm histologically the presence of KS, post-baseline biopsies were not specified or required by any of the study protocols but were included in the protocols as an optional procedure. As it turned out, we have essentially no data from the study regarding post-baseline biopsies. In fact, in the North American study, only 3 percent of patients had any biopsy on-study, and the phase 1-2 study was 6 percent of patients. We learned that some of these biopsies were done for completely unrelated purposes but were, nevertheless, filtered in through the case report form retrieval process. We did have just a couple of patients from the phase 1-2 study where they had a biopsy where the biopsy appeared to be in an area where KS had been noted previously, and there was a suggestion, a very strong suggestion, of clearing histologically, but bottom line is what I am telling you is I really do not have

a body of data from the studies comparing pre and post data.

In answer to your first question, in terms of mechanism of action, I would like to ask Dr. Andres Negro-Vilar to come up and respond to that.

DR. NEGRO-VILAR: Thank you. There is a number of evidence that have been published regarding the mechanism of retinoids, and many of the cytokines and growth factors that Dr. Miles mentioned that are potentially involved in Kaposi's sarcoma growth. We have one piece of data in terms of the activity of alitretinoin in this, if we can show the next slide, please, for a minute.

I have to say also that the mechanism is complex, involving a number of factors. These are cell cultures that we had from AIDS Kaposi's sarcoma derived cells, treated in vitro with alitretinoin in yellow. You can see the cells here. We measured in two different ways how this compound will affect cell growth and proliferation. One was looking at thymidine incorporation, and you can see a very nice dose related activity there. The second one was to look at the direct cell count, and also there we saw a very nice dose response with increase in concentrations of the drug. As a control, we used a human umbilical vein endothelial cells that are not proliferating actively, and those were not affected by the treatment.

We know that retinoids affect both IL-6

production, IL-6 receptor, a number of other cytokines, as Dr. Miles had mentioned, basic fibriglos growth factor, N-CAMS(?), a set of molecules that are important in the growth and proliferation of some of these cells. I cannot tell you there is a single mechanism responsible for these, but certainly there is a lot of recommendation in the literature that supports that retinoids such as alitretinoin have activity in a number of the growth factors that contribute to the growth of these cells.

I do not know if Dr. Miles would like to add something to that.

DR. MILES: I do not think I have anything further to add to that. I did want to address one comment that you did make, Michael, and that had to do with the CD4 count at presentation. As you know from the most recent AMCOO2 study, the median CD4 count at presentation for naïve KS patients was 242, with a range from 13 to 703. So I think the statement that patients are generally presenting with lower CD4 counts with their KS today is probably not really accurate.

There is, in fact, probably something going on with the protease inhibitors, and whether patients are presenting now with KS with higher CD4 counts in spite of antiretroviral therapy may be the case, but we do not really have enough data to say one way or the other in that regard.

DR. DUTCHER: Dr. Simon?

DR. SIMON: Two questions. One, on the international study, the target sample size was 270 patients, and the interim analysis was planned after 78 patients. How was that 78 selected? Why was that?

DR. HOLDEN: Dr. Yocum, do you want to address that issue?

DR. YOCUM: To try to get at the heart of your question, the question was why we ended up with 82 patients instead of 78 patients?

DR. SIMON: No, why was the interim analysis planned after 78 patients in a study of 270 patients?

DR. YOCUM: I am sorry. I misunderstood the question. But Dr. Thomas Moon, our biostatistician, will respond to your question.

DR. MOON: The shortest answer is that the protocol specified that as the interim sample size to look and was based largely on comparison of proportions of approximately 10 versus 50 percent, as specified in the protocol. The derivation of that was something which we inherited when we saw the protocol.

DR. SIMON: Second question, did you do any analyses to look at the relationship between Kaposi lesion control and systemic status of HIV disease?

DR. HOLDEN: Are you specifically referring to

perhaps level of virus that was present in the individuals?

DR. SIMON: Yes. For example, did some patients have progressive HIV disease, and did those patients who went on to the open-label phase of this study, the American study, tend to have less durable KS response?

DR. HOLDEN: We have limited information on the viral load in these studies, but I think Dr. Yocum can address that particular question.

DR. YOCUM: I have tried to characterize what the extent of antiretroviral therapy use was during the study. The protocols were designed to collect CD4 counts over the duration of the study. I think it is slide 579. While we are cueing that up, I would like to point out that the HIV viral load tests were not readily available in the time frame that these studies were initiated, and therefore we have very little to know viral load data from these studies, but perhaps I can answer your question looking at the CD4 count in the studies for the North American study. Looking at the blinded phase, Panretin gel in yellow and vehicle gel in white, we were looking at the change in mean CD4 count over weeks on study, and I think the conclusion here is that we cannot attribute responses to any meaningful change in the CD4 count during the duration of the study.

DR. SIMON: That does not really show that, because you would have to show for the patients who were

having a CD4 response whether they tend to have a better KS response. This does not show that at all.

DR. YOCUM: I can address that point in another slide. Slide 578, please? Actually, perhaps we can show 577 and slide 578.

This shows for the North American study the comparative response rates for Panretin gel versus vehicle gel as a function of the baseline CD4 count -- that is, CD4 at time of entry -- and in each of these partitions, 0 to 50, 51 to 100, 101 to 200, and greater than 200, the response rate in Panretin gel exceeded that for vehicle.

If I can go to the next slide, we look at the response rates for patients looking at the CD4 count at the time of onset of response.

DR. SIMON: I guess what I was trying to get at is, you know, once you get beyond the 12-week double-blind period, it is very difficult to interpret the data about the durability of the lesion control. I was really trying to distinguish between whether it really is an effect of the Panretin gel or whether it could just be effect of the control of the systemic disease having an effect on the control of the KS. These slides do not really get at that at all.

DR. YOCUM: Well, as you know, I cannot show you comparative data beyond the initial blinded phase.

DR. SIMON: No, I was not looking for comparative data. I would just take the patients on the Panretin gel and divide them into those who had progressive systemic disease at some point and those who did not and see whether that sorts things out in terms of what their KS progression was.

DR. YOCUM: So you would be perhaps postulating that responses were durable or that we accrued additional responses because there was some degree of immune reconstitution beyond the initial blinded phase?

DR. SIMON: Correct.

DR. YOCUM: That postulate, of course, would require -- when I showed you the CD4 count over the initial blinded phase -- that there was something occurring beyond that point that we were not seeing during the 12 weeks.

DR. SIMON: Well, you claimed clearly that there was an additional effect beyond 12 weeks on response to Panretin gel, and I am trying to evaluate how to interpret that.

DR. YOCUM: I understand that, sir.

DR. DUTCHER: For example, could you show a stable dose of antiviral medication for six months before or six months after? Were they on the same doses of medication so that the only new event was the addition of the gel?

DR. YOCUM: I could show you data of that nature

for the initial blinded phase. We are actually comparing treatment arms, if that would be helpful.

DR. ABRAMS: Could we just look at slide 579 again that you just showed us? I think that will get to this point that Dr. Simons tried to make a little bit. I just noticed on that slide that you have a CD4 rise, and it looks to me -- what we are asking is how responses to Panretin or vehicle correlate with the change in the mean CD4 cells. So, i.e., do the patients who have a benefit in CD4 cells, are they the same ones that are having the benefit in response to the Panretin? What we see here in the vehicle patients over 12 weeks is a 20 CD4 cell rise, starting with a mean CD4 of 120. That is better than we get with most antiretroviral interventions, suggesting to me that there is a little bit of a background antiretroviral activity effect going on here.

The fact that you do not have viral load in an era of protease inhibitors is a little bit confusing, because that is how we measure protease inhibitors. So I think viral load information should be present in this same patient population. Viral load even at San Francisco General Hospital has been available during the time course of this study. This is disturbing that there is a 20 CD4 count rise over 12 weeks in the vehicle group, and a similar rise probably in the Panretin group. I do not know why it

dropped back down to baseline at week 12, but I would be curious to know why that happened on that slide.

DR. YOCUM: Well, perhaps to point out the obvious, that if the CD4 count is rising for vehicle, that is only going to tend to cause an increase in response rate for vehicle and would reduce the additive response rate, the treatment effect, and reduce the level of significant difference between the treatment groups. I was not personally impressed with the 20 change in CD4 count, but perhaps Dr. Miles could had another clinician's perspective.

DR. MILES: Perhaps we could look at another trial which was reported in the same population, Andrew Carr's(?) study in patients with KS who were given Ritonavir for a period of 16 weeks. There the baseline CD4 count was 142 mean, and there was a mean increase over 16 weeks of 166 CD4 cells, and in that setting there were no clinical responses to therapy. So while you are talking about a significant increase of 20 cells, I think when we talk about improvements in antiretroviral therapy and increases in CD4 counts, we are generally looking at much larger increases in CD4 counts than 20.

DR. ABRAMS: You know as well as I know that when we do a study, a clinical trial, on patients who are not on an active agent that you do not expect a CD4 count rise over a short 12 week period, usually. If you can show me a

clinical trial where there has been a CD4 count improvement in patients on the control arm over a short 12 week period, I would be curious to know what that is.

DR. MILES: Do we for a fact know whether this is statistically significant, Richard?

DR. ABRAMS: The question really hearkens back to that we know the CD4 change over this period. So the question that Dr. Simon was asking, I believe, is how does that correlate with the responses to the Panretin, and that should be something that you should be able to tease out, I think. How does the CD4 and response to the Panretin correlate?

DR. MILES: If you followed that argument logically, you would not be able to explain the responses in two of the four patients who presented today who are not on antiretroviral therapy, nor would you be able to explain the responses for the individuals who are not receiving antiretroviral therapy on the study, albeit the few that are not on this particular study. There are still clinical responses in the patients who are on zero antiretroviral therapy. So although it is a very small number, there are some. So it is difficult to explain it entirely by that mechanism, but I cannot discount your hypothesis.

DR. ABRAMS: And patients who are not on antiretroviral therapy may have changes in their immune

function and viral load, just spontaneously as well, just depending on what else is going on in their lives with other concomitant infectious processes, et cetera, as you know.

DR. DUTCHER: Could you perhaps comment on what happened to the systemic KS in the patients that had systemic KS that were on this agent and whether there was a -- I mean, obviously there is no absorption or a very minimal absorption of this agent, but it is a disease where certainly the life-threatening problems have to do with visceral organ involvement, and did you see, for example, stabilization of skin disease but progression of systemic disease with KS in these patients?

DR. YOCUM: It is a good question. As you recall, I think it was 12 and 16 percent or so of the patients had known visceral disease at the time of entry in the study. There were no specifications in the protocol for baseline or post-treatment evaluation of visceral disease, because we were not anticipating a systemic effect from the drug, but we found, though, that clinicians are reluctant to subject patients to the invasive procedures that are necessary to assess visceral disease. We found that to be true even in our studies of oral alitretinoin, and after discussions with investigators in designing the studies, it was recommended against making any attempts to try to bronchoscope or endoscope patients to try to identify baseline or track

visceral disease. So what I presented is known visceral disease at baseline, and I have no data to show you regarding what happened to visceral disease in those patients after exposure to drug.

DR. SCHILSKY: I just wanted to ask a follow-up question to that. What happened -- or maybe you can tell us how many patients who did not start the study with visceral disease developed visceral disease while on the study and how you handled those patients in the analysis. I mean, some of them undoubtedly went on and got chemotherapy and other things that may have confounded the subsequent analysis after visceral disease developed.

DR. YOCUM: I naturally recorded the reason for withdrawal of patients from the study, and there was a category of progressive disease, and then we have subcategories for progressive disease in the treated lesions, progressive disease in the treated non-index lesions, progressive disease in non-treated lesions. So that information was recorded. Any patient that -- as I said, the data I have shown you are the intent-to-treat population of patients. So regardless of the reason for withdrawal, the patient would have been included in the analyses I have shown you.

DR. TEMPLE: You have heard the rebuttal already, but you have not actually heard from Dr. White about why he

was interested in looking at beneficial response. As I understand it, one of the reasons was that he did not think any of the other measures of improvement took account of the negative skin effects of inflammation and so on. So my question to you is did the physician's global assessment look only at the sort of KS lesions as KS lesions, or did they attempt to take into account the whole appearance of the skin. From reading the description of it, it looks like they were focused on the lesions and not on the inflammatory surround.

DR. YOCUM: The protocol specified guidelines for the utilization of the physician's global physician's subjective assessment was to consider the change from baseline -- that is, the degree of improvement or worsening -- in all of the lesions that were treated with gel, and that would be both index and non-index lesions. So I guess what you are asking is was the physician's global a risk-benefit assessment or just a response assessment.

DR. TEMPLE: Yes. Yes, you could have a global that says how is the patient doing, or you could have a global that says how are the patient's KS lesions, all of them, not just the index lesions, doing? Those are two somewhat different things. Maybe you need to ask the investigators.

DR. YOCUM: I think I might do that, because the

concept was that this would be a response assessment, degree of improvement with regard to the treated lesions. There were no guidelines in the protocol as to whether they would consider the other side of the equation. So while I have only a small sampling of investigators, we could perhaps hear from Dr. Melosky and Dr. Bodsworth.

DR. MELOSKY: The global assessment, as specified by the protocol, was to look at the KS lesions in the patient, but not only the index lesions but other lesions that the patient was applying the gel to. So if the patient was not applying the gel to a lesion on the arm but was applying to all other lesions, those were the lesions that you did your global assessment to.

If a patient had progressive disease during the course of your observation, the gel being applied may be applied not at the same time as the baseline of the study, but in reference to your question, it was to the KS lesions that the patient was being applied the gel to.

In reference to the other question about systemic disease, there were several of my patients with pulmonary KS, as well. As an oncologist, those are watched carefully, and chemotherapy was not given to any of my patients because they did not progress systemically, although may have progressed in their cutaneous disease.

DR. TEMPLE: Just to be specific though, if a

patient had improvement in what appeared to be the KS lesions, and the inflammatory response was such that the person looked quite terrible, that could still be considered a good response.

DR. MELOSKY: I think that the inflammatory response is being a little overplayed. The actual inflammatory response was perhaps pinkish rash around the lesion. It was both satisfactory to the clinician and to the patient.

DR. BODSWORTH: I would like to concur, too. We were asked to look at the response of actual tumor mass. I think the interpretation of the irritation did differ very much, in fact, from investigator to investigator and from the North American study onto the other study. I personally tended to discount a great deal the effect of the inflammation, being aware of the natural history of irritation of the skin, which is to settle fairly readily after you discontinue the drug, which is indeed what we saw.

DR. DUTCHER: If there are no further questions for the sponsor, we are going to take a 10 minute break, 15 minute break.

[Brief recess.]

Agenda Item: FDA Presentation

DR. WHITE: Good morning. I am Dr. White, and I am going to be presenting the FDA's presentation. This is a presentation for Panretin topical gel 0.1 percent, and the NDA was submitted by the Ligand Pharmaceuticals Company from San Diego, California. This is the FDA review team that reviewed this application, and the disciplines included medical, chemistry, pharmacology, toxicology, biopharm, biometrics, and my special thanks goes out to our consumer safety officer, Amy Chapman, who coordinated all these disciplines.

Now the FDA will not repeat Ligand's presentation. I will reintroduce the proposed indication and compare response criteria for systemic therapy for KS and topical therapy for KS. The two pivotal phase 3 trials will be discussed.

The first pivotal trial, study 31, I will present the efficacy data and show photographs to provide our perspective of the efficacy. I will present safety data and show photographs to provide a perspective of the dermal toxicity at the application site for this topical agent.

For the second pivotal trial, study 503, I will give a brief comparison of the important difference between study 31 and study 503. Since study 503 was stopped based on the interim analysis for efficacy, I will provide

information relative to the interim analysis. I will then present the efficacy data. Photographs for this study were of poor quality. I think one example will be presented. After this, I will present a summary of what I have said.

The proposed indication for topical Panretin is for first-line topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma. Recall that DaunoXome is approved as a first-line cytotoxic therapy for advanced HIV-associated Kaposi's sarcoma.

The response rates with topical Panretin are not comparable to the response rates produced with systemic therapy for a number of reasons. First, for systemic therapy, all lesions or lesions in a selected region of the body are counted and evaluated. For topical therapy, in this NDA, only a minimum of six lesions are required as index lesions for evaluation of height and area reductions.

Second, with systemic therapy, the appearance of new lesions, which often prevents a response from being declared, confirmed, and prolonged, new lesions are not considered progressive disease with topical therapy. In study 31, in the total population of patients, 131 patients, or 49 percent, developed new lesions since baseline. For the Panretin responders, at least 22, or 47 percent, of the patients developed new lesions during the trial. In contrast, in trials with systemic therapy, new lesions would

have interfered with the declaration, confirmation, and prolongation of a response.

Progressive disease was scored only in the treated index lesions for Panretin. Also, for nearly all the index lesions raised at baseline, progressive disease by flat lesions becoming raised cannot occur in trials of topical therapy.

Fourth, in the Panretin pivotal trials, progressive disease in the treated lesions was required to be confirmed in four weeks. Systemic therapy, in trials of systemic therapy for KS approved by the FDA, this was not a requirement for progressive disease.

Overall, a response rate for Panretin topical gel is inflated when compared to the response rates for systemic therapy.

There were two pivotal trials submitted to support this NDA. The first trial was a 238-patient trial, the North American trial, started in April of 1996 and ending in July of 1997, and the title is shown here on this slide. This study will be referred to as study 31.

The second trial was a European, United States, and Australian trial. Two hundred and seventy patients were planned for accrual. The study started in September of 1996 and was stopped in September of 1997 after an interim analysis on the total of 82 patients, and the title of this

trial is also shown on this slide. This trial will be referred to as study 503.

Now let's go back to the first pivotal trial. This slide shows the response that we see of Panretin gel compared to placebo or vehicle gel. These results were generated in the first 12 weeks of the blinded phase of the study. Using a modification of the ACTG criteria, the six index lesions were assessed for height reduction from a plaque to flat or from a nodule to plaque or from a nodule to a flattened lesion. The six index lesions were also assessed for a 50 percent reduction in the area. New lesions, progressive disease in treated non-index lesions, and progressive disease in untreated lesions had no impact on the response rates.

Forty-seven, or 35 percent of the Panretin patients in the blinded phase had a response of the treated index lesions, according to the modified ACTG criteria, and there was one complete response. Twenty-four, or 18 percent of the vehicle patients in the blinded phase had a response. The p-value for this, for this endpoint, was .002. The FDA confirmed that 46, or 34 percent, of the Panretin patients in the blinded phase had had a response, and there was one CR, and 22, or 16 percent of the vehicle patients had a response.

Now, according to the physician's global

assessment, an assessment of the treated index lesions and the treated non-index lesions, 26, or 19 percent of the Panretin patients had a partial response. Five, or 4 percent, of the vehicle patients had a response. The p-value was .00014.

The FDA reviewed the photographs for cosmetically beneficial responses. During the blinded phase, 20, or 15 percent, of the Panretin patients had a beneficial response. Five, or 4 percent, of the placebo patients had a response, a beneficial response. The p-value was .0026. Cosmetically beneficial responses will be defined in a later slide.

Ligand also reported that the patients' overall satisfaction with the KS-lesion drug effect favored Panretin, and the p-value for this was .0001.

The disparity between the modified ACTG response and the physician's global assessment is noted. This table for the Panretin responders showed that about two-thirds of the partial responders by the modified ACTG criteria were evaluated as stable disease by the physician's global assessment.

This slide attempts to explain the disparity between the modified ACTG response and the physician's global assessment. I divided the 47 Panretin responders into two groups. One group responded by a reduction in the height of index lesions only. The second group responded by a

reduction in area of index lesions, a more potent criteria, plus or minus reduction in the height of index lesions. Only 5 out of the 33, or 15 percent of the modified ACTG Panretin responders scored with height reduction only, agreed with physician's global assessment. Interestingly, 11 out of the 14, or 70 percent of the modified ACTG Panretin responders scored with area reduction, agreed with the physician's global assessment. A similar pattern is seen with the vehicle arm. It appears that the physician investigators were impressed with the area reduction as a response criteria. However, since the physician investigators were to assess both the treated index lesions and the treated non-index lesions, the disparity between the modified ACTG response and the physician's global assessment may mean that the activity seen in the treated index lesions and scored by the ACTG response was not evident in the treated non-index lesions.

Now, the photographs. The FDA had indicated to Ligand that photograph evidence would be very helpful in our review of the NDA and that FDA would depend on this information. Ligand responded that they had taken this into account and provided a uniform photographic system to all sites in their phase 3 study. Ligand outlined for their investigators very meticulous procedures for the required photography of patients' treated index lesions. These

procedures included, one, the same image size for the lesion on the slide; two, the same orientation of the lesion on the slide; three, the lesion in the very center of the slide; four, a sharp focus on the lesion; five, the label at the very top of the slide; and six, the label to contain the correct information. All rolls of films were sent to Canfield Scientific(?) in New Jersey.

In support of these procedures, Ligand had sent a memo to their study coordinators of study 31, stating, quote, photography of the patients' index lesions is very important documentation of the patient's response to treatment in this phase 3 study, end of quote.

To assess the effect of Panretin on the disfiguring effects and cosmetic problems of KS, I will turn to the photographs. These pictures from baseline through response should provide evidence for the benefit of a Panretin response in these KS patients. In assessing the photographs for beneficial response, the FDA looked for a 50 percent improvement in the appearance from baseline, considering the KS lesion and dermal toxicity at the lesion site.

Fifty percent of the index lesions were expected to improve in appearance. For the blinded phase analysis 12 weeks, if the response started by 12 weeks, the response confirmation would occur after that 12 week point. The

improvement was to be maintained at least 3 to 4 weeks.

I will present photographs from 3 groups of responders by the modified ACTG criteria. The first one will be the best Panretin beneficial responders. The second one will be Panretin responders not considered beneficial responders by the FDA, and three, the best placebo beneficial responders. I will not present photographs from non-responders.

Now I will present four of the best Panretin beneficial responders. Now, the procedure I am going to follow in presenting the photographs, only patients Ligand considered a responder will be presented. Again, no non-responders will be presented. All the index lesions will be presented, one lesion at a time. The response score indicated at the top of the slide refers to the total score for all index lesions and does not necessarily refer to the individual lesion shown on the slide. I will provide the baseline character of each lesion -- that is, whether it was raised or flat -- and this is information from the case report form. This will not be necessarily an FDA opinion of what is on the slide. I will also provide information about the type of response the patient had according to the case report form, for example, whether there was a reduction of the height of the lesion, a reduction of area, or disappearance of the lesion.

I will also point to the approximate time in the photographs when the response was reported to occur. I will indicate dermal toxicity.

After showing all six slides, I will also indicate what the physician investigator thought, that is, the physician's global assessment. I will indicate that the patient satisfaction with those KS lesions treated at the time the response occurred, and finally I will also have on that slide the FDA assessment for cosmetically beneficial response.

The first patient with beneficial response to Panretin is case number 242. Out of the six index lesions, there were three plaque lesions at baseline. By the ACTG criteria, a partial response was scored when all three of these lesions became flat. Also, the combined area of the six index lesions was reduced by 50 percent. This is lesion number 1, which was a plaque at baseline, and this became flat at 4 weeks. This is according to the case report form. This is the investigator's assessment. FDA does not necessarily agree based on the photo. The lesion at 8 weeks measured 0 by 0 according to the case reports form, and the investigator called this grade 2 erythema at 4 weeks.

This is some more, the additional slides on patient lesion number 1.

This is lesion number 2, which is also a plaque at

baseline. It became flat at 4 weeks, and it measured 0 by 0 at 12 weeks. This is just more on lesion number 2.

This is lesion number 3 which was a plaque at baseline, and it became -- it was scored on the case report form as being flat at 4 weeks, and there was grade 1 erythema for this lesion reported on the case report form. Lesion number 3 continues.

Lesion number 4 was flat at baseline, and there was no other anti-KS activity reported on the case report form, and this was considered grade 1 erythema. Lesion number 4 continues.

This is lesion number 5, which was flat at baseline, but at 12 weeks the measurement was 0 by 0, and there was grade 2 erythema seen at 4 weeks. Lesion number 5 continues.

Lesion number 6 was also a flat lesion at baseline, and it measured 0 by 0 at 12 weeks. And this is other slides from lesion number 6 so you can see what happened in this patient.

By the modified ACTG criteria, there was a partial response. By the physician's global assessment there was a partial response, and this patient was moderately satisfied. In terms of the beneficial response, yes, there was. It is also of note that the response in the KS lesions of this patient may have possibly been due to a protease inhibitor

effect. It appears that the KS lesions started to disappear after Crixivan was started.

This is patient number 682. This patient had six plaque lesions at baseline. Four lesions became flat.

This is lesion number 1, which is a facial lesion. This little pad is covering the patient's eye, and I believe that this is the plaque lesion at baseline. This became flat at 8 weeks, and grade 1 erythema was only scored at week 2. This was scored as erythema 0, if it is indeed erythema.

This is lesion number 2, which was also a plaque at the baseline, and this became flat at 8 weeks.

This is lesion number 3, which is on the other side of the patient's nose, and this was a plaque at baseline, and the area became reduced by half at 8 weeks, and there was no erythema.

This is lesion number 4, which was a plaque at baseline, and it became flat by 12 weeks, and the area was also reduced by half in comparison to baseline, and there was no erythema.

This is lesion number 5, which was also a plaque at baseline, and by 20 weeks it became flat.

This is lesion number 6, which was a plaque at baseline, and there was no recorded anti-KS activity.

Now for this patient, by the modified ACTG

criteria, there was a partial response. By the physician's global assessment, there was stable disease, and the patient was moderately satisfied with the response. According to the FDA, there was a beneficial response.

Now the FDA felt obligated to present Ligand's best responder, and that is case number 292, a complete responder. There were six plaque lesions plus one nodule lesion at baseline. All the lesions became flat, the area became reduced, and this was considered a complete response.

I believe here is lesion number 1, which was nodule, and by 8 weeks it became flat, and the measurement was 0 by 0. There was grade 2 erythema seen at 8 weeks and grade 1 erythema at weeks 12 and weeks 16. This is lesion number 1 continued.

This is lesion number 2, which was a plaque at baseline, became flat by 4 weeks, and measured 0 by 0 at 4 weeks, and there was grade 2 erythema at 8 weeks and grade 1 erythema from 12 weeks through 28 weeks.

This is lesion number 3, which was a plaque at baseline. It became flat by 4 weeks and measured 0 by 0 at 4 weeks. There was grade 2 erythema at 8 weeks, grade 1 erythema at week 4, and also grade 1 erythema from week 12 throughout week 28. And lesion number 3 continued.

Lesion number 4 was flat at baseline, measured 0 by 0 at 8 weeks. There was grade 2 erythema at 4 weeks,

grade 3 erythema at 8 weeks, and grade 1 erythema from weeks 12 through 28. What happened to lesion number 4 is continued.

Lesion number 5 was flat at baseline, but the lesion measured 0 by 0 at 4 weeks. There was grade 2 erythema at 8 weeks and grade 1 erythema at 4 weeks, and from week 12 through week 28 -- this is information from the case report form.

This is lesion number 6, which was a plaque at baseline. It became flat by 4 weeks, measured 0 by 0 at 4 weeks. There was grade 2 erythema at 8 weeks, and again, there was grade 1 erythema at week 4, and from week 12 through 28.

By the ACTG criteria, there was a complete response. By the physician's global there was also complete response, and the patient was very satisfied with the response, and, yes, there was a beneficial response in this patient.

The next patient is patient number 379. Now unfortunately there were no baseline photographs submitted with the original NDA. We asked the Ligand people about that, and it turns out that those photographs were of poor quality. But anyway, I will show it anyway.

There were six plaque lesions at baseline. All of these lesions became flat, and the area became reduced.

This patient for lesion 1 had a plaque lesion at baseline, and this is on the patient's forehead. You can see the eyebrows here. By 4 weeks it became flat, and then the area was half. You can see how that is continuing on. There was grade 1 erythema from week 2 through week 12.

This is lesion number 2 on the side of the patient's nose, which was a plaque. Excuse me. I do not have a baseline. But this became flat by 8 weeks, and you can see the difference, and there was grade 1 erythema from week 2 through week 12.

This is on the other side of this patient's face, for lesion number 3, and there was a plaque at baseline. That became flat, which I suppose is this here, at 8 weeks, and there was grade 1 erythema from week 2 through week 12.

This is lesion number 4, which is also a plaque at baseline. There was no other evidence of anti-KS activity for this lesion, but there was grade 1 erythema from weeks 2 through 12.

This is lesion number 5, which was a plaque at baseline, became flat by 4 weeks, and there was grade 1 erythema again from week 2 through week 12.

This is lesion number 6, which was a plaque at baseline and became flat at 2 weeks, and there was erythema from week 2 through week 12.

This patient, by the modified ACTG criteria, had a

partial response. By the physician's global there was also a partial response, and the patient was very satisfied with their response. The FDA thought that there was a beneficial response.

Now I am going to present some patients that the FDA did not believe had a beneficial response.

This is patient 121 who had six nodule lesions at baseline, and all of these lesions became plaques. This is lesion number 1, which was a nodule at baseline, and it became a plaque at 4 weeks, and this is, again, according to the case report form, and there was grade 2 erythema at week 4 and week 8, and there was grade 1 erythema at week 2 and 12, and this was rated as 0 erythema at week 14.

This is lesion number 2, which was a nodule at baseline, which became a plaque at 4 weeks. There was grade 2 erythema at week 4 and 8, and I guess from what is shown on the slide, there was grade 0 erythema at week 14.

This is lesion number 3, which was a nodular lesion. It became a plaque at 4 weeks, and there was grade 2 erythema at 4 weeks and 8 weeks, and this was scored as 0 erythema at 14 weeks.

This is lesion number 5, which was also a nodule at baseline. This became a plaque at 4 weeks, and there was grade 2 erythema at 4 weeks and 8 weeks, and this was graded as 0 erythema at 14 weeks.

Also a nodular lesion at baseline for lesion number 6. This became a plaque at 4 weeks, grade 2 erythema at 4 weeks and 8 weeks, and this was scored as 0 erythema at 14 weeks.

By the ACTG criteria, this patient had a partial response. By the physician's global assessment, there was stable disease. Relative to patient satisfaction, the patient was neutral, and no, there was not a beneficial response.

This was patient number 771. This patient had three plaque lesions at baseline. One became flat, and then the six lesions at first I thought became nodular; on the case report form, a lesion was scored as 0 if it was flat, 1 if it was a plaque, and grade 2 if it became nodular, but on the case report form these lesions became grade 3.

This lesion was a plaque at baseline. It became flat at 4 weeks, and then at 12 weeks this grade 3 height, something above nodular, appeared. There was grade 2 erythema at 4 weeks and grade 3 erythema at 8 weeks and 12 weeks.

This is lesion number 2, which was a plaque at baseline. It became flat at 4 weeks. Then it became a plaque again at 8 weeks, and then this grade 3 height elevation happened at about 12 weeks. There was grade 2 erythema at 4 weeks, grade 3 erythema at 8 weeks and 12

weeks.

This is lesion number 3 which was a plaque at baseline. There was no evidence of any anti-KS activity, but there was grade 2 erythema at 4 weeks, and there was grade 3 erythema at weeks 8 and 12, and then they also had this grade 3 height elevation.

Lesion number 4 was a plaque at baseline. There was grade 2 erythema at 4 weeks, grade 3 erythema from weeks 8 through 14, and there was no other evidence of anti-KS activity.

This is lesion number 5, which was flat at baseline and remained so, and then the erythema is obvious on the slide.

This is lesion number 6, which was flat at baseline, and there was no other evidence of anti-KS activity, and the erythema is obvious on the slide.

Now for this patient, if we step back from the index lesions, because these are not lesions, these are patients that we are treating -- if we step back we have a better perspective of what is occurring in the patient. This is the legs of this particular individual at baseline here and at 11 weeks, and the following index lesions -- this is lesion number 3, 4, and 6, I believe -- which you also need to note that the erythema that is evident in this patient also indicates the non-index lesions that were

treated. That is just for information purposes.

For this patient, there was a partial response by modified ACTG. Physician's global assessment was stable disease. The patient was very satisfied with the response, and no, there was no beneficial response.

This is patient number 247, and this patient had lesions on their foot, selected from the foot. There were four raised lesions at baseline, and two of these lesions became flat.

Again, this is, I think, on the top of the patient's foot. This is lesion number 1, which was a plaque at baseline. The case report form reported it became flat at 4 weeks, and the area was halved by 12 weeks. There was noted on the case report form grade 2 erythema at 4 weeks and 12 weeks.

This is lesion number 2, which was a plaque at baseline. It became flat by 8 weeks, and the area was halved at 16 weeks, and I am sorry I do not have a slide for 16 weeks, but that was information on the case report form.

Lesion number 3 was a plaque at baseline, became flat at 4 weeks, and the area was half by 16 weeks.

This is lesion number 4, which was flat at baseline. The area of this lesion became half by 16 weeks, but there is no slide for that.

Lesion number 5 was flat at baseline. There was no evidence of anti-KS activity.

Lesion number 6 was flat at baseline, and there was no evidence of anti-KS activity.

This patient had a partial response by the modified ACTG criteria, by the physician's global assessment there was stable disease, and with regard to the patient's satisfaction, with the KS lesions treated the patient was neutral. No, there was no beneficial response.

This is patient number 383. There were four plaque lesions at baseline, and all four of these lesions became flat. Oh, and also, there were no baseline photos submitted in the original NDA, and we asked Ligand about that, and we agreed the photographs were of poor quality. So I will not be showing them.

This patient had a plaque lesion at baseline, which became flat by 4 weeks, and there was no erythema.

This patient had a plaque at baseline which also became flat at 4 weeks, and there was no erythema.

This is lesion number 4, which had been a plaque at baseline and became flat by 8 weeks, and there was no erythema.

Now, for this lesion, week 4 is the incorrect lesion. You know, my being from New Jersey, I look at that as the state of New Jersey. I guess, the Ligand people would think it looks like the state of California, but there was no recorded activity, and if you focus on this, you will

see that these week 4s have been reversed. Here is the state of New Jersey there. There was no anti-KS activity for this lesion on the case report form.

For patient number 383, there was a partial response by the ACTG criteria. There was stable disease by physician's global assessment. The patient was very dissatisfied with their response, and there was no beneficial response.

This is patient number 469 who had three plaque lesions at baseline, and all three of these became flat.

This is a plaque at baseline which became flat at 4 weeks and continues on. They scored grade 2 erythema at 8 weeks.

This is lesion number 2 which was a plaque at baseline. It became flat by 4 weeks, and there was only grade 1 erythema scored at 4 weeks. This was not graded as erythema on the case report form. It may have been graded as something else.

This is lesion number 3, which was a plaque at baseline, became flat by 4 weeks, and there was grade 2 erythema as scored on the case report form at week 8.

This is lesion number 4. In this case, the lesion -- I am not sure which one it was -- was flat at baseline. There was no other evidence of anti-KS activity, and there was grade 2 erythema scored at week 8.

Lesion number 5 is the same. It was flat at baseline. There was grade 2 erythema at week 8. There was no other evidence of any anti-KS activity.

This is lesion number 6, which was -- I am not sure where it is on this slide. Anyway, there was no evidence of any anti-KS activity on the case report form, and grade 2 erythema was graded at week 8.

For this patient, there was a partial response by the modified ACTG criteria, stable disease by physician's global, and the patient was moderately satisfied, and no, there was no beneficial response, at least according to the FDA.

Now I am going to show the best responses to placebo.

This is patient number 4. This patient had 3 plaques and 3 nodules at baseline. All these lesions had height reductions in the lesions, and I want you to note the acne that you can see in these photographs between weeks 4 and week 8. It turns out the patient was taking anabolic steroids.

This is lesion number 1, which was a plaque at baseline, and this is one of those placebo patients that went beyond the 12 weeks. So this became flat by 20 weeks. Note the little acne lesions that you can see in the photograph.

This is lesion number 2. This is the nipple here, and this is a nodule adjacent to it, and this became a plaque at 4 weeks, and the area was halved by 20 weeks, and this continues.

This is lesion number 3, which was a nodule at baseline. It became a plaque in 2 weeks and was gone by 16 weeks.

This is lesion number 4, which was a plaque at baseline, became flat by 8 weeks, and was gone by 16 weeks.

Lesion number 5 was a plaque at baseline. The area was halved by 8 weeks, and it was essentially gone by 16 weeks.

This is lesion number 6 which was a nodule at baseline, became a plaque within 2 weeks, and was gone by 8 weeks. Now there is a note that Crixivan was started in this patient about one week before the response was started.

This patient, by the modified ACTG criteria there was a partial response, by the physician's global there was also a partial response, and the patient was moderately satisfied, and yes, there was a beneficial response.

This is patient number 679. This patient had three plaques at baseline, and all three of these became flat.

What you see here is lesion number 1, which was a plaque at baseline, became flat -- I do not have a slide --

became flat at 2 weeks, but it continued on.

Lesion number 2 was a plaque at baseline, became flat within 2 weeks, and the response continued.

This is lesion number 3, which was a plaque at baseline, became flat within 4 weeks, and the flatness continued.

This is lesion number 5, which was flat at baseline, and there was no evidence of any anti-KS activity on the case report form.

This is lesion number 6, was flat at baseline. There was no other evidence of anti-KS activity.

Also, in this patient, it is of note that there were protease inhibitor changes while on study at about 1 month to 2 months while on study. There were changes in protease inhibitors with Crixivan and Saquinivir.

This patient by the modified ACTG criteria had a partial response. By the physician's global assessment there was stable disease, and patient satisfaction was neutral, and yes, there was a beneficial response.

This ends the FDA's presentation of the photographs for beneficial responses in study 31.

Now relative to safety -- we will move on to safety in study 31. The table in this slide is reproduced from the results reported by Ligand. All adverse events with an incidence of greater than 5 percent at the

application site were reported. The number of patients represents both the initial blinded treatment plus blinded crossover patients. Rash at the application site was the predominant toxicity.

Now if you move down the slide here to skin disorder, Ligand has already told us skin disorder includes items like excoriation, crusting, scab, cracking, drainage, eschar, fissures, and oozing.

Now, back up to rash, 75 percent of the patients on Panretin developed rash at the application site compared to 12 percent of patients on placebo. According to the adverse events of the case report forms, rash appears to be erythema. Based on this, the FDA explored the incidence of severe dermal activity in patients exposed to topical Panretin.

Now, the case report forms reported local dermal toxicity in at least two sections -- grade 3 treatment-limiting toxicity at the local dermal site and erythema at the index lesions being evaluated by the investigators for response, and you can see that pretty much so they are about the same. Where grade 3 was local irritation and/or the lesion, the skin became very red with edema with or without vesiculation, and I am also including, since the investigators have scored these, grade 2 erythema which was increased redness and possible erythema.

Treatment-limiting toxicity. Twenty-eight patients, or 12 percent, had grade 3 dermal treatment-limiting toxicity. These patients were Panretin patients, either during the blinded phase or the open-label phase, and also vehicle patients who were crossed over to Panretin or who were treated with open-label Panretin. The median time to the first treatment-limiting toxicity was 8 weeks, with a range of 2 weeks to 32 weeks.

Now the investigator evaluating the KS response also had a place on the case report form where they could score erythema, and there were nine Panretin patients, or 7 percent, had grade 3 erythema during the initial blinded phase. The median time to first grade 3 erythema was also 8 weeks, with a range of 4 to 12 weeks. There were 66, or 49 percent, of patients on Panretin who grade 2 erythema during the initial blinded phase. The median time to first grade 2 erythema was 4 weeks, with a range of 1 week to 8 weeks.

If you look further in the case report form under adverse event, for grade 3 erythema there were 21 patients on Panretin, or 9 percent, with grade 3 erythema. So what I did is then I just combined these and just counted common to patients once, and what you end up with is 35 patients, or 16 percent of patients, having some sort of grade 3 toxicity while on Panretin.

Now, it is of note when you look at this 16

percent that when the FDA looked for beneficial response, 17 percent of the Panretin patients had a cosmetically beneficial response.

Now this is the foot of patient 463, and I am only going to show you lesion 2. This patient is not considered a beneficial response by the FDA, and for your information at baseline, I guess this was considered a plaque which then became flat and continued to be flat for 4 weeks. In the physician investigator's evaluation of this lesion, no erythema and no edema was scored in the case report form.

This is patient 628, lesion number 5. For your information, this patient was a partial responder to Panretin, was not a beneficial responder. The lesion was flat at baseline and there was no evidence of any anti-KS activity, according to the case report form, and there was grade 1 erythema at weeks 2, 4, and 12, and there was grade 2 erythema reported in the case report form at week 8.

Now, to the second pivotal trial, study 503. This was a European, United States, and Australian trial. Two hundred and seventy patients were planned for accrual. The study started in September, 1996, and was stopped in September of 1997 after an interim analysis, and the title again is shown here on the slide.

There are important differences between this study, study 503, and study 31. First, the entry criteria

and evaluation of the study primary endpoints in study 503 is not as rigorous as study 31. In study 31, a minimum of six cutaneous KS lesions, including at least three raised lesions, were required for entering on study. A response could be scored by a reduction in the height of the index lesions, a reduction of the area of the lesions, or disappearance of the lesions. In contrast, for study 503, at least three lesions were required for study, but raised lesions were not required. A response could be accrued here also by reduction in the area of the lesion, disappearance of the lesions, and reduction in area of the lesions only if the lesions selected were raised.

Second, in study 31, global photographs were required at evaluation points. Global photographs were not required in study 503, and no investigator took global photographs in study 503.

Without global photographs, verification of the number of non-index lesions treated and evaluated during the study could not be ascertained. FDA verification of the physician's subjective assessment of index and non-index lesions was impossible.

Third, in study 31, patients applied the study drug three times daily. The frequency of application was increased according to protocol specifications to four times daily as tolerated and was decreased to twice daily, once

daily, or every other day according to toxicity. In study 503, patients applied the study drug two times daily or less.

Now this slide, the next slide, explains the chronology of events leading up to the submission of study 503 as a pivotal trial. In August of 1997, Ligand informed the FDA that study 503 met the interim analysis criteria for early stoppage. Now originally, study 503 was to be submitted to the European regulatory authorities, and this study had planned to accrue 270 patients. This study was stopped based on the first 82 patients.

At a meeting between Ligand and FDA in October of 1997, Ligand informed the FDA that study 503 was strongly positive, and at another meeting between FDA and Ligand in December of 1997, the FDA was then informed that the interim analysis boundary was miscalculated in the protocol.

Now the interim analysis for efficacy was performed on 82 patients, 36 and 46. It is of note that the next 52 patients accrued were equally balanced, with 26 patients accrued to each arm. The protocol originally specified a p-value of .005 as the level of significance for early stopping. The p-value achieved at the interim analysis was .00027, by Fisher's exact, and the Chi-square, for information only, is also shown. However, recalculation of the interim analysis p-value by Ligand approximately

after the study was stopped revealed that a p-value of .000025 was the required p-value for early stopping. The FDA's calculation of the interim analysis p-value by Lan-Zucker is also shown.

However, according to the protocol, 39 patients to each arm were planned for analysis, i.e., 78 patients. The interim analysis shown here was performed as specified in the protocol, as well as we took three Panretin patients accrued to the second cohort to get to 39. The interim analysis level shown here does not meet the early stopping rule.

Now again, the protocol specified that 39 patients in each arm was planned for analysis, or 78 patients. Now in this table, what we did is we took the interim analysis results for the first 78 sequentially accrued patients, and again, the interim analysis level of significance for early stopping was not met.

All right, this is the efficacy results of study 503, and the FDA reviewed for this -- what we did is we reviewed the data listings on the patients and the individual index lesions, and this is data that was entered and checked off by the physician investigators. The physician's subjective assessment, which appears to be the same as physician's global assessment, is also shown, as well as the patient's subjective assessment.

The FDA's assessment, including beneficial response, are also shown. Beneficial response has already been defined in the early part of this presentation. The efficacy results presented here are the data used in the interim analysis.

Now according to Ligand, 15, or 42 percent, of the Panretin patients in the blinded 12-week phase had a response of treated index lesions. This is according to the modified ACTG criteria. There was one complete response. Three to seven percent of the vehicle patients in the blinded phase also had a response. The p-value here was .00027. It is of note that 15 of the 36 patients, or 42 percent of the patients on Panretin, and 15, or 32 percent, on vehicle had no raised lesions at baseline. The reduction of area, a more rigorous response criteria, was the only criteria available to score a response in these patients. Sixty-seven percent of the responders, whether on Panretin or placebo, had index lesion area reduction alone or in combination with height reduction as the criteria for response.

Now the FDA confirmed that 14, or 39 percent, of the Panretin patients in the blinded phase had a response, but there was no CRs, and 3 to 7 percent of the vehicle patients had a response. The p-value here was .00062.

According to the physician's subjective

assessment, an assessment of treated index and non-index lesions, 17, or 47 percent, of the Panretin patients had a partial response, and 5, or 11 percent, of the vehicle patients. The p-value here was .0003.

The FDA reviewed photographs for cosmetically beneficial responses. During the blinded phase, 7, or 19 percent, of the Panretin patients had a beneficial response, and 1, or 2 percent, of the vehicle placebo patients. The p-value here was .019.

According to the patient's subjective assessment, 47 percent of Panretin patients had a partial response, and 11 percent of the vehicle patients scored a partial response according to the patient.

Safety. According to the access database, there were 4, or 11 percent, of Panretin patients had severe skin toxicity. For all severity of skin toxicity, 26, or 72 percent, were affected. For all severity of rash, there were 15 patients, or 42 percent of the patients, on Panretin.

I will not show a series of photographs for study 503, and in contrast to study 31, the quality of photographs here was much poorer, but for information, this is lesion D for patient 438, a complete responder by Ligand, using the modified ACTG criteria, and as shown here, a whole series of lesions and one photograph, lesions C, D, E, and F.

Summary. The FDA expected a patient population with early KS for which systemic therapy was not indicated. The NDA has patients with extensive KS and patients with prior systemic treatment. Complete information was provided in the NDA only on the index lesions.

Panretin gel responders cannot be compared to responders with systemic treatment. First, only index lesions were evaluated with Panretin by the ACTG criteria; second, progressive disease, which often interferes with responses to systemic therapy, was much harder to achieve in the Panretin trials; third, new lesions in the Panretin trials did not interfere with the response to Panretin.

The FDA agreed with Ligand's tumor responses by modified ACTG. In the photographs, however, the responses by modified ACTG were not cosmetically beneficial in about 50 percent of the patients. Erythema and edema obscured the improvement in some responders. After the edema subsided, the KS lesion appeared to be visible in these responders.

The erythema may have frustrated efforts to blind this study. This may explain why very few patients crossed over from Panretin to placebo in the blinded phase of this trial. In study 31, the rates for the physician's global assessment and the cosmetically beneficial responses were in close agreement. In fact, also in study 31, cosmetically beneficial responses was 17 percent, and grade 3 skin

toxicity was 16 percent on Panretin. Similarly, in study 503, cosmetically beneficial response was 19 percent, and severe skin toxicity was 11 percent on Panretin.

Study 503 was less rigorous than study 31. There were less rigorous entry criteria -- i.e., raised lesions were not required. However, more rigorous response criteria, area reduction, was the basis for most responses, and the interim analysis was questionable.

This ends my first presentation with PowerPoint.

DR. DUTCHER: Thank you very much.

Are there questions from the committee for Dr. White?

Dr. Krook?

DR. KROOK: One question, I guess, would be when a new lesion arose, Bob, was it treated? I suspect it was.

DR. WHITE: Well, the only thing I could tell was from looking at the global photographs, and what I could see, if they were on Panretin, was a red spot that was not there prior.

DR. KROOK: And the second is a little bit of a comment as a practicing physician is that it is nice to see that the global assessment of the physician and the FDA agree.

[Laughter.]

I mean, we commonly, at least in medical oncology,

look at chest x-rays, measure this, measure that, and I think it is the overall assessment, and I heard the sponsor say and some of the clinicians say that they looked just at the lesions and tried to make this -- obviously there was a global assessment here, also.

Thank you.

DR. DUTCHER: Dr. Simon?

DR. SIMON: I think I am just confused about something. On one of your last slides, you are talking about erythema may explain why in study 31, 2 of 38 Panretin patients crossed over to vehicle. What is the 38?

DR. WHITE: Oh, apparently there were about 30 or 35 patients who withdrew who were taking -- who did not get to the 12-week period, and then those patients were offered crossover, and I think only two on Panretin crossed over to vehicle, but 15 on vehicle crossed over to Panretin.

DR. SIMON: Did you review any photographs of patients who crossed over?

DR. WHITE: No. No.

DR. SCHILSKY: This is just a question about criteria, because, you know, the FDA's assessment of response, using the modified ACTG criteria, was pretty close to the sponsor's assessment of response, which suggests to me that those criteria at least are reproducible, but your assessment of patient beneficial response obviously led to a

substantially lower assessment of response than using the ACTG criteria, and, as Jim pointed out, tended to agree more with the physician global assessment. So I guess my question to you is even though the ACTG criteria appear to be reproducible, it also appears that they may not really be useful in this clinical setting, and I wonder if you would agree to that or if that is what we should be inferring from this presentation.

DR. WHITE: Yes, when the FDA reviewed the modified ACTG criteria, all we were reviewing is what the investigators were checking off on the case report form and whether or not what got translated into responders was indeed. So again, I have no idea what the physician investigators saw. The closest way I come to seeing what the physician saw in these patients is the photographs, and I tried to show enough of the photographs to give you an idea.

DR. DUTCHER: Dr. Abrams?

DR. ABRAMS: Just to comment on that, the ACTG criteria are 10 years old, and they were produced because there were no real criteria. The ACTG is no longer doing KS studies. I think it is probably imperative that this committee challenge the AIDS Malignancy Consortium, the group now currently doing KS studies, to come up with some criteria that are more meaningful.

MR. MARCO: If I could give a point of information -- I do not know if maybe somebody from the FDA wants to speak about this, but the AIDS Malignancy Consortium, in conjunction with FDA, has, not only using these old classic tumor endpoints, have come up with some soft endpoints that are going to be looking at beneficial response, whether it be color, pain, edema, and so on, and I think they are being piloted right now in one of our studies. So that is very important, and it is a good point.

DR. DUTCHER: Dr. Temple?

DR. TEMPLE: Bob, tell me if you do not agree with this, but one should not think of the responses as preferable or not preferable. They are asking different questions. It may be reasonable to look at any particular lesion and see if it shrinks, you know, much the way we look at lesions in systemic therapy, but that does not necessarily tell you how much benefit the patient has obtained from it, and the global is one way of getting at that, and as Bob said, actually being able to look at pictures is our only way of finding out what is going on, because we are not at the bedside.

DR. DUTCHER: Dr. White, can you give us any sense of the impact of retroviral on these two groups, the placebo and -- I mean, you have pointed out in the placebo group that a couple of the responders had just started a new

protease inhibitor, but do you have a sense of -- could you get a sense from the data of how that impacted on both groups?

DR. WHITE: You know, I tried not to use that to influence whether or not I was going to call something a response. I knew Dr. Abrams was going to ask me about that, so that is why I did such a detailed analysis, but it seemed when I was looking at patients and looking at the global photographs in certain areas of the patient's body where I knew that they were not being treated with Panretin because there was no redness in the skin, lesions appeared to be disappearing, and it coincided with changes in protease inhibitors, and for some of them I thought it may have been something else, and I asked Ligand about it, and they confirmed that I think the person was using a corticosteroid cream, and then they documented exactly where the patient was using it, and it was not on the area where I thought KS lesions were indeed disappearing.

DR. ABRAMS: I did just want to thank you and congratulate you for the sense of impact of protease inhibitor analysis that was in our background material. I thought it was very useful.

DR. WHITE: Thank you. I did not know if I had done it right, but I tried to be fair. I did not just take -- you know, I tried to use as much information that was

available in the NDA.

DR. OZOLS: Could you comment on why you think some of the patients were satisfied with the treatment when it seemed from the photographs that we would really question why would they be satisfied with the results of some of those treatments?

DR. WHITE: That was a real problem for me, because the way I did the review, I tried to have as much information in front of me. I had the listings in journal of how the patient responded. I had the individual lesions. I had the photographs in front of me. I had the CD4 levels at baseline. Also, when the response was confirmed, because I knew all the responders would have shared that time point in common, and then I also pulled up the patient satisfaction when the response was confirmed, and for some of them that were very satisfied, based on what I could see in the photograph, I have no idea. I ended up spending more time chasing around those patients trying to figure out what they were seeing.

Now, you may be able to speculate that with all this redness that the patient is seeing, they may interpret that as being activity and something good and then with time they may become disappointed, but I do not know.

DR. DUTCHER: Dr. Krook?

DR. KROOK: Just for the audience, not the

clinicians, who are here, again, in medical oncology we can give drugs and as long as people get sick, they think they are getting better. I mean, that has happened time and time to me. If I do not get the nausea and I do not lose my hair, the drug is obviously not working, and I think some of this has to be the same thing. The perception of the redness as an improvement. I do not know why, but we all see it. That is all I am saying.

DR. SCHILSKY: I guess just another question about the use of the photographs, because as other topical therapies are developed, the utility of photographs in evaluating the treatment is likely to be in question again. You know, as all these pictures flew by us, I guess my global assessment, if you will, is that the photographs did not seem to me to be particularly useful in confirming response, but it did appear that they were useful in documenting progression, and I wonder if you would agree with that, having spent a lot more time looking at these.

DR. WHITE: Yes, it seemed it was harder to see whether somebody was responding, but it was pretty much easy to see when somebody was doing poorly, and Ligand, I mean, they did an excellent job in terms of the photographs in study 31. I know they are going to be quoting me endlessly in subsequent meetings, but they were really good.

DR. DUTCHER: Any other questions for Dr. White?

[No response.]

Thank you. Good job on PowerPoint.

[Laughter.]

Any discussion before we address the questions? Comments?

[No response.]

Agenda Item: Discussion of Questions to the Committee

No? All right. So we will proceed with the questions. If you look at the summary that was in the blue folder, it is actually a table of one of the slides that Dr. White showed us with the varying tumor response in the North American study during the initial 12 weeks based on ACTG criteria, physician's global assessment, beneficial response, photographs, patient overall satisfaction, and then the summary table where he showed best response, where partial response by ACTG may have been translated into stable disease from the physician's global, and then the same summary table for study 503, and then the summary table with the adverse events.

So it is a summary of the data, and then the questions are, number one, is Panretin gel effective for first-line topical treatment of cutaneous lesions in patients with AIDS-related KS? I guess to discuss this particular question, the issue of first-line versus where

does this agent fit into the treatment of cutaneous KS probably deserves some discussion before a vote.

Dr. Krook?

DR. KROOK: My own feeling is that I do not think that we have seen at least the same tables of other first-line. What I have heard is radiotherapy, I have heard injections, and perhaps other people in the room have others. So I have problems with the first-line. I could be comfortable with the topical treatment, and I think you leave it to the clinician as to whether this would be second, third, or fourth. I think one could look at all the first-line, which somebody, which the company put up, and then like we do again in medical oncology, sit down and talk about, hey, the potential timing. I could see using this as a first-line, but I do not think we have seen anything that says that this is better than radiotherapy, better than some of the other modalities.

DR. DUTCHER: I do not know if all of you had a chance to read this position paper that was handed out also from the Treatment Action Group, but one of the comments that they make is that KS is not acne. It is a systemic disease and a malignant disease. So how does a topical treatment fit into the treatment of something like this?

DR. KROOK: Well, I also think as long as the mike is on that it has been brought up that cutaneous lesions are

not the only thing in AIDS-related illnesses, and I think it has to be used in place. As this is written, there may be other things that somebody would want to use. That is my problem with first-line.

DR. DUTCHER: Dr. Abrams?

DR. ABRAMS: With regard to your comment just now about using a topical therapy for a systemic disease, particularly in malignancy, I grappled with that a bit myself and then recalled mycoses femboides(?) and nitrogen mustard. In fact, I have a family member who has been in and out of remissions for the past 10 years doing that topical application. The difference is I think we have a better understanding of how that might work, and one of my concerns about this is that there is -- you know, it is unfortunate that we do not really have a lot of information with regards to mechanistic aspects of how this in fact could work. I do think that the company deserves to be congratulated for integrating much of the FDA's comments over the course of the review of this application into the design of the current protocols that we have been looking at.

I brought up before my concern about the word first-line, the word in there, and I think, you know, it does also have some activity in other places. My concern with first-line would be that people who are uninformed in

treatment might just think that this would be the automatic first thing to use in patients with KS, and that probably without careful evaluation of the patient would not be a good idea.

DR. OZOLS: That is really a difficult issue. This committee wrestled and saw some very impressive data before with systemic treatments for disseminated KS, and saw some very dramatic responses. So I guess really the question would be when do you make that cutover between extensive KS that some of these patients had here on this study to try to use a local treatment when you really would be using a systemic treatment which, of course, has its own toxicity as well? I mean, those are clinical decisions which are often very difficult.

DR. ABRAMS: Again, that is often driven by the patient, and no real intervention has been demonstrated to prolong survival with regards to whatever the KS lesions themselves do. I just saw a patient last week, first time, came to me, just discharged from the hospital with pneumocystis, which is very unusual in this day and age, with a CD4 count of 10, has been diagnosed HIV-positive for 12 years, never sought any therapy, claimed that he was a procrastinator, and came in, had a single KS lesion on his cheek in my initial evaluation of him last week. Obviously, he is a patient with some denial, not a patient in whom I

would want to do something particularly taxing, and wondered if this might be a patient where application of this gel might be beneficial.

However, again, seeing this information today, I was hoping that he could do it for 2 weeks and it would disappear. It seems like maybe 52 weeks and having a big red spot on his cheek, and I am confused really, if that is an appropriate patient, but there are patients -- and again, this has to be worked out with the patient -- who would choose to have a topical local treatment, because they are adverse to systemic cytotoxics or otherwise.

MS. BEAMAN: At the same time, I reflect on the four gentlemen who spoke this morning with the emphasis that they put on cosmetic effect and the interaction and relationship discontinuance in their lives, and I think that if this is indeed helpful in the psychological and the aesthetic effect, then certainly it is well worth looking at.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: I would also agree with that, and I do not think we have seen anything nor imagined any scenarios here that would suggest that patients who have access to this kind of treatment, which the company is not claiming is anything other than superficial benefit, have gone on to develop more life-threatening problems, either

due to their disease or due to the therapy, because they were doing this, nor is it likely to happen, because dermatologists do not tend to treat AIDS patients. Patients with AIDS are treated by internists and infectious disease specialists who know how to balance the various aspects of their treatment.

DR. ABRAMS: And occasionally oncologists do.

[Laughter.]

DR. DUTCHER: Mr. Marco?

MR. MARCO: Well, I think Dr. Krook's first question was very important, for the reason being is first-line or not first-line, and first-line topical. I do not know if anybody has truly done a review of data for radiation for KS, cryotherapy, or intralesional velband(?). You know, in the late 1980s or early 1990s, there were response rates anywhere from 65 to 90, but lord knows what criteria they were using. You know, are the toxicities as extreme? I do not want to use the word extreme, but do you see so much inflammation, do you see it resolving quicker than, say, your 24 or 52 weeks? I do not know. I mean, I do not treat KS. Donald, maybe you can talk about your patients that have had radiation or velband.

DR. ABRAMS: I mean, the response is much more immediate, but I agree with your analysis that none of these other modalities, including liquid nitrogen, have drug

pharmaceutical company sponsorship to get a new drug application. So we have not had very rigorous evaluations of the response rate to those initial therapies.

DR. SCHILSKY: Just one other comment. I do not disagree with anything that has been said. There must be some marketing strategy for having the words first-line in there that I do not appreciate, because I do not see any reason to include them. If they were just removed from the indication, then certainly that would not preclude the use of this therapy as first-line treatment.

You know, obviously there were patients in these studies for whom this was first-line therapy, and they did not seem to do necessarily better or worse than any other patients who were in the study. They were a minority of the patients in the study. The studies were not designed to enroll exclusively patients for whom this was first-line therapy, and so including the words first-line in there suggests, leaves the suggestion that the studies were actually done in patients for whom this was first-line therapy, which was clearly not the case. So my own view would be to drop out the words first-line. That would still allow it to be used in that setting, but it would not sort of offer the suggestion that that was the group that was actually studied.

DR. DUTCHER: Dr. Abrams?

DR. ABRAMS: Plus, in this era of medical economics, people who use it not as first-line might not be able to be reimbursed.

DR. KROOK: John, since I started some of this, I do not have any problem -- I guess I am saying that I guess there other therapies that could be chosen as first-line. This could be first-line. We have done this thing where we have said drug X is a second-line when X fails. That is not what I guess I am saying. Simply, the absence of the word first-line would make it acceptable to me.

DR. DUTCHER: I think that that should be the question, because I do not think we have even defined a sequence of hierarchy of different treatments. I think we have defined niches for certain approaches. I mean, painful feet lesions would probably not want to wait several months, whereas something that is visible might. So then we should ask the question, is Panretin gel effective for topical treatment of cutaneous lesions in patients with AIDS-related KS?

Okay, who would like to answer that question? Dr. Krook?

DR. KROOK: As it is worded, I would recommend voting yes.

DR. BUTCHER: Okay, all those who would vote yes?

[Show of hands.]

Eight.

All those who would vote no?

[Show of hands.]

One.

The second question, is the safety of Panretin gel acceptable in view of its efficacy and in view of available alternative treatments?

Who would like to comment on that question, comment on the safety issues?

DR. ABRAMS: In view of topic alternatives again, this being the sixth that will be available, it is probably not the easiest, but certainly this committee has dealt with agents that have much more significant toxicity evaluations. So I would say that the answer to that is probably yes, as well.

DR. DUTCHER: I think that the issue, if we were to decide that for this particular niche use this is approvable, there would need to be some statement saying this is not systemically absorbed, this is not systemic treatment, we have no data on systemic effects, because what you do not want to do -- clearly, if it is useful in certain situations, it may not be useful in other situations, and that needs to be specified, I would think.

DR. KROOK: I would agree with Dr. Abrams. I think the photographs actually lend to this. People

obviously had extensive redness and we were -- as my colleague were talking, we were just seeing the one lesion, and sometimes if you just see the whole system it is better, but certainly the people who were in the trial put up with a lot of erythema. So they obviously did it. They obviously did not stop. So my answer to that would be yes.

DR. DUTCHER: All those who would vote yes on question number two?

[Show of hands.]

Eight yes.

No?

[Show of hands.]

One no.

Do you want to make a comment?

MR. MARCO: I just basically, in seeing the slides, I think it really solidified it for me, seeing the erythema, seeing how long it lasted. The safety over the effectiveness, the 35 percent chance -- I will give it 35 -- over the benefit response of 19, 35 percent chance of a 50, 5-0, percent reduction over that period of time with that much erythema. I cannot see how the risk benefit comes out towards the drug or towards the patient, especially if they have to stay indoors because of the intense redness from the inflammation.

DR. DUTCHER: I do not think they have to stay

indoors.

MR. MARCO: I am not saying stay indoors. No, what I am saying Janice is that it would possibly be used by somebody because of a disfiguring lesion, and I can understand that, and local therapy should be used for things like that, but to replace that disfiguring lesion with something with a large red mark that lasts up to 2 weeks, 4 weeks, 6 weeks, with pain that lasts for a few weeks, I just do not think it is worth it.

DR. DUTCHER: Okay, but I think the rest of us are voting yes in terms of these as a potential option to have people have an option, if they so choose.

So in question number three, is this Panretin gel NDA approvable?

All those who would vote yes?

[Show of hands.]

Eight yes.

All those who would vote no?

[Show of hands.]

Eight yes, one no.

If so, should the cosmetically beneficial response rate based on photographs be included in the package insert?

Dr. Krook?

DR. KROOK: Obviously, if you pick the right photos, you can sell anything. I think if I looked at Dr.

White's photos or actually the company's, I think the biggest problem would be choosing. I would vote no on this one. I think experience with the clinician and the patient will decide how long they do it and how many people.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: Well, I think the question could also be raised as to whether the safety and the expected toxicity should also be included as a photograph, and perhaps those could be some of Dr. White's carefully selected photos that showed both the intense erythema, followed by a good lesion response -- might take care of both.

DR. DUTCHER: Dr. Simon?

DR. SIMON: It did not ask whether photographs should be included, but rather whether the response rate based on the photographs should be included, and I would think that might be a good idea, because it does sort of give a sort of more balanced view of the erythema relative to the response of the lesions themselves.

DR. DUTCHER: Dr. Abrams?

DR. ABRAMS: I would agree with that, and I do not think you actually can put -- can you put photographs in a package insert? I do not think you can?

DR. DUTCHER: Dr. Temple, can you put photographs in a package insert? Not easy to do, right?

DR. TEMPLE: I do not think that has ever been done, but photographs have certainly been included in promotional materials accompanying drugs. I mean, the thing about pictures, I guess, is that everybody likes to believe them when they show benefit and they are skeptical when they do not. It is very hard to know how to pick things that would be representative. I feel fairly sure that promotional materials for this product will have some pictures in it. I do not have a shadow of a doubt about that.

[Laughter.]

DR. DUTCHER: Well, I think the key is that the beneficial response and the physician's global assessment mesh, and I think you have to put those criteria in versus the ACTG which our experts here have already said are somewhat out of date. So I think if we do not trust the best percentages based on just measurement changes, we need to put the whole picture in the package insert.

DR. TEMPLE: So perhaps you are suggesting an emphasis on the physician's global?

DR. DUTCHER: Well, I think both should be.

Dr. Ozols?

DR. OZOLS: Well, I think the two summary tables that were put together are very good, and I would put those right in.

DR. DUTCHER: The two that are included in this handout. And I think also some statement that it is not treatment for visceral disease.

Any other comments on question number four?

[No response.]

Ended early. Are we going to vote on that one? All right, we will vote on number four. Should the cosmetically beneficial response rate based on photographs be included in the package insert? All those who would vote yes?

[Show of hands.]

Nine yes, no noes.

All right, thank you very much. We will take an hour for lunch and be back here probably about -- want to come back at quarter to 2? Okay, 15 minutes before 2 for the afternoon session.

[Whereupon, at 12:45 p.m., a recess was taken until 1:30 p.m. that same day.]

A F T E R N O O N S E S S I O N (1:45p.m.)

DR. DUTCHER: So if everyone could take their seats, we are going to begin the afternoon session. We are going to begin the afternoon session with the open public hearing, which in fact will be a videotape by Roxine Reade, and there is also a handout of this available at the front desk, a transcript.

Agenda Item: Open Public Hearing

ROXINE READE (Videotape): I would like to thank you for the opportunity to tell you about my experience with DepoCyt. I am a 47-year-old cancer patient. I was first diagnosed in March, 1994, with an adenocarcinoma of unknown primary. I was initially treated with 6 cycles of an experimental four-drug chemotherapy program by intravenous injection and entered a complete remission that lasted for almost 20 months.

In March, 1996, I began experiencing excruciating headaches, blackouts, and a progressive loss of vision, and on April 15 of that year, I was diagnosed with neoplastic meningitis when malignant cells were found in my cerebral spinal fluid. I was found to have a renal carcinoma and tumor involving my ovaries at the same time. Although my prognosis appeared very bleak, Dr. Kurt Jaeckle offered me the chance to participate in the controlled trial of DepoCyt versus methotrexate while I simultaneously underwent

versus methotrexate while I simultaneously underwent intravenous chemotherapy with Taxol, Carboplatin, and 5FU. Unfortunately, I was randomized to receive methotrexate, which was administered twice a week through an Ommaya reservoir in my head. Even with the twice weekly dosing, I rapidly became debilitated. I suffered severe headaches after the treatment, and I could literally feel my body growing weaker. Methotrexate did not stop the progression of my neoplastic meningitis, and I lost vision to the point where I could not read. I developed problems with my bladder and bowels, and I was confined to a wheelchair because of back pain and weakness in my legs.

The schedule of treatment with methotrexate was grueling. I am from a small rural state where medical treatment often entails long distance travel. I had to fly on a small plane twice a week from South Dakota to Houston, leaving at 7 am and returning around midnight every Tuesday and Thursday. Looking back, I can at least feel fortunate that my injections could be done through an Ommaya reservoir. I cannot even imagine how terrible it would have been if I had had to get these injections into my spine on a prolonged basis. I had great difficulty physically from the side effects of methotrexate and emotionally dealing with the twice weekly treatment schedule. At one point, I wanted to quit and give up, but Dr. Kurt Jaeckle encouraged me to

continue until he could switch me over to DepoCyt. It is very difficult to maintain a tolerable quality of life if you are constantly getting treatment twice a week. Even systemic chemotherapy gave me a three-week break between sessions, allowing me to recuperate and return to my normal daily routine.

Because my symptoms were getting worse during the methotrexate treatment, once the protocol permitted, Dr. Jaeckle switched me over to DepoCyt. Following just two doses of DepoCyt, my CSF cytology went from positive to negative, and the neurological problems caused by the disease improved. Neurologically, I returned to normal status with no apparent damage. I was able to read again, and the fact that I only had to go to Houston every other week permitted me to return to work and to a much more normal lifestyle. This was truly a gift, for even during the time I was receiving DepoCyt, my husband and I were able to spend some really wonderful time together doing things that gave enormous meaning to my life.

I received a total of 6 injections of DepoCyt, and this succeeded in putting me into a remission. The cancer elsewhere in my body was controlled with the intravenous chemotherapy that I received at the same time. My remission lasted for 16 months until November of 1997 when the recurrence was discovered on a routine cytology check. Dr.

Jaeckle restarted me on DepoCyt, and this time it was the only chemotherapy I was receiving. DepoCyt is by far the easiest treatment in terms of adverse side effects and toxicity I have received since my original diagnosis. I was never precluded from engaging in my normal day-to-day activities during the course of treatment with more than 6 cycles of DepoCyt. Within 5 to 6 hours of the time Dr. Jaeckle administered the DepoCyt, I was on a flight home. My CSF cytology returned to negative after two treatments. The only unpleasant side effect of treatment that I experienced was weight gain from the steroid therapy that accompanied the DepoCyt doses. Thus, after I failed to respond to methotrexate, DepoCyt saved my life twice.

Every form of cancer therapy has moderate to severe side effects. This is something that each patient must consider when deciding on treatment. However, it should be the cancer patient's decision as to what he or she can tolerate in order to survive and maintain an acceptable quality of life. I wonder how many patients would be standing here today with me if their physicians had had access to DepoCyt? How many patients would have continued treatment if they could have been treated every other week instead of having to get injections twice a week? I firmly believe that I would not have survived my cancer as long as I have without DepoCyt.

I mentioned that DepoCyt has saved my life twice. I am hoping that it can save my life a third time, for I have just found out that my CSF cytology is again positive after 11 months in my second remission. Cancer is a very frightening disease, but it is far more frightening to be denied access to a drug that has saved or prolonged your life as DepoCyt did mine. Despite its success in controlling my cancer, the FDA had decided not to approve DepoCyt for patients like me. I know that you will be considering whether to support approval of DepoCyt today. I also know that the only that DepoCyt will remain available to me and other patients like me is for you to support its approval for some type of disease, because no company can continue to produce a drug for just one patient. I respectfully ask you to consider that those of us with this terrible disease who have received DepoCyt, generally tolerated it well, and in some of us its effectiveness has made an enormous difference in our lives. Ours is a rare disease and we have very few treatment options. Please give us one more. Thank you.

DR. DUTCHER: Just for the record, Ms. Reade has sent a letter saying that she has no financial association between herself and DepoTech Corporation. At her request, DepoTech arranged without cost to have this videotape made.

Before we go on to the sponsor's presentation,

there are some new people at the table. So perhaps we will just introduce new members of the committee starting with our patient representative.

MS. KROVASIK: My name is Susan Krovasik, and I am from Austin, Texas.

DR. DUTCHER: Thank you. And the FDA people?

DR. WILLIAMS: Grant Williams, medical team leader.

DR. VAN DE VELDE: Helgi van de Velde, medical reviewer.

DR. DUTCHER: Thank you. All right, we will now proceed with the sponsor's presentation.

Dr. Howell?

Agenda Item: Sponsor's Presentation: DepoTech

DR. HOWELL: My name is Stephen Howell, and I am a professor of medicine at the University of California, San Diego, where I run the cancer pharmacology program for the UCSD Cancer Center. I am also functioning at the moment as the medical director of the DepoTech Corporation, and we are pleased to be here this afternoon to present the DepoCyt NDA to you and would like to express our sincere thanks to the staff of the FDA and to all of you for undertaking a very rapid review of this NDA.

I am accompanied today by a number of experts who are available to answer questions regarding the disease and

its treatment, including Dr. John Holcenberg from the University of Washington, Dr. Sandra Horning from Stanford University, who is chairman of the ECOG Lymphoma Committee, Dr. David Poplack, director of the Texas Children's Cancer Center and someone who has dedicated much of his career to the development of new drugs for the management of neoplastic meningitis. Unfortunately, Dr. Judith Ochs, who was to be here today, is unable to attend because of an event this morning at her company that she is now working at. She was the ODAC representative who participated in working out the DepoCyt development plan back in 1992.

We also have some of our investigators with us today, including Dr. Michael Glantz, from the University of Massachusetts; Dr. William Shapiro, who is chairman of neurology at the Barrow Neurologic Institute in Phoenix and former chairman of the Brain Tumor Study Group, and another person who has played a very prominent role over the years in defining the management of these patients; Dr. Kurt Jaeckle who Roxine referred to unfortunately again was to be here but is unable to attend because he just had a baby, and that took precedence.

Now DepoCyt is indicated for the intrathecal treatment of lymphomatous meningitis, and we are asking you to consider a rather challenging situation here this afternoon. The first challenge is that this is a very small

pivotal trial in a rare disease. We knew it would be a small pivotal trial when we started the project back in 1992, but we proceeded with it with the encouragement of the staff then at the FDA, and the trial that we worked out with their input they felt would be considered an adequate and well-controlled trial, given the rarity of the disease and the complexity of the clinical situation.

The second challenge that we face is that as new personnel replaced the original personnel at the FDA, the FDA opinions as to what is needed for approval has changed. It has been a long time since 1992.

Also, as you will see this afternoon, the FDA has changed its opinion about how response should be assessed in these trials.

Now, despite the rarity of lymphomatous meningitis, we should be trying to develop new treatments for this disease. However, the data sets that we will be able to generate will always be small and incomplete, not because of incompetence on the part of the physicians or the investigators but because of the clinical complexity of the cases. Fortunately, Congress has provided the FDA with a mechanism for dealing with these situations, and it is the mechanism of accelerated approval, and we are seeking such an accelerated approval for this orphan indication on the basis that DepoCyt produces an effect on a clinical endpoint

-- in this case response rate -- that is reasonably likely to predict patient benefit in a life-threatening disease.

Now, as you know, accelerated approval is different from standard approval in that it is conditional and may require additional documentation of activity.

Now what hurdles do we have to jump over to make DepoCyt eligible for accelerated approval? First, response, as defined in the DepoCyt studies, has to be considered a surrogate endpoint that is at least reasonably likely to predict clinical benefit. Second, DepoCyt must produce responses in lymphomatous meningitis, and third, the safety of DepoCyt must be acceptable in the context of the life-threatening nature of the disease and the benefit afforded by the drug.

So why are we here today? We are here today because the difference in response rates in the pivotal study has now reached such divergence that there is no reasonable expectation that accrual of additional patients would result in the loss of the difference that has already been obtained. The FDA specifically invited the submission of this NDA after reviewing the data on DepoCyt for the treatment of lymphomatous meningitis that you will see today.

I will point out in passing that no drug has ever been formally approved for the treatment of lymphomatous

meningitis and no new drug has been brought into clinical practice in more than 30 years.

This was a very difficult trial to do, and there are two ways of looking at this. We did not get all the information that we had originally sought. One can take one approach of focusing on the deficiencies in the data set, looking at all the things we said we would do in the protocol and in the end could not do, or one can celebrate the fact that a randomized trial has finally been done in a rare and difficult disease and that it provides evidence that these patients can effectively be treated with many fewer injections of a reformulated established drug.

Well, DepoCyt is a reformulation of cytarabine. It is a sustained release formulation in which the cytarabine is encapsulated in particles made up of phospholipids and cholesterol. These particles are approximately 20 microns in diameter, and the drug is in the aqueous chambers inside this ball of foam. When the ball of foam is suspended in a vial of normal saline, the final product looks like skim milk and has that consistency and can be easily injected, even through a very fine needle, into the body. When this is stored in a refrigerator, the drug stays inside the ball of foam, but when the drug is injected intrathecally, the particles spread out throughout the neuraxis and slowly release the ara-C. The lipid

particles themselves are very well tolerated.

Now the cytotoxicity of ara-C is a function of both its concentration and duration of exposure, and I am giving you example here of a melanoma cell line, a human melanoma cell line studied in vitro. When you use just a 2-hour exposure, even if you use very high concentrations of drug, you do not get very much tumor cell kill, but as you prolong the duration of exposure for longer and longer periods of time, the concentration survival curves get progressively steeper and steeper, and using a 72-hour duration of exposure, you obtain a full 2 logs of tumor cell kill.

This principle has been demonstrated in a very large number of experimental systems, including human cell lines in vitro, as well as the NCI 60-cell panel, where exactly the same change in cytotoxicity as a function of duration of exposure was well demonstrated, in vitro sensitivity assays of fresh human tumors, human tumor xenograft systems, and of course it has been documented in man, and it is the principle that is the basis for the use of 5 to 7 day continuous infusions of ara-C for the treatment of leukemia.

Now the problem that we face in patients with lymphomatous meningitis is that the tumor infiltrates the meninges around the brain and spinal cord and also gets into the CSF and spreads throughout the neuraxis. So treatment

must be directed at the entire neuraxis. When we inject free ara-C into the lateral ventricle or the lumbar sac, the drug is cleared so rapidly from the CSF that it does not get a chance to spread out evenly throughout the whole neuraxis, leaving some areas undertreated.

One of the advantages of the DepoCyt formulation is that the particles themselves spread out well throughout the neuraxis. Here is a graph showing the particle count in the ventricles shown in pink and the lumbar sac shown in yellow, following intraventricular injection of 75 milligrams of DepoCyt. You can see the particle count in the ventricle drops very rapidly, and the particle count in the lumbar sac raises very rapidly, and they equilibrate in less than 24 hours. Thereafter, the particle clearance from both ends of the neuraxis is equivalent.

This is a compartmental model of the pharmacokinetics of DepoCyt. When DepoCyt is injected into the CSF compartment, the particles spread throughout the neuraxis and slowly release ara-C, maintaining free ara-C concentrations in the CSF, with a half-life of 141 hours.

Now some of this drug does leak out of the CSF, but when it does, it gets diluted in the plasma compartment in a very, very much larger volume -- so concentration is low -- and it is very rapidly cleared from the plasma compartment with a half-life of 10 minutes. So the total

drug exposure for the systemic compartment is orders of magnitude lower than has been well-documented in man to cause any degree of myelosuppression, and, in fact, using normal assays one cannot detect any measurable ara-C concentration in the plasma.

These are the actual pharmacokinetics of injection of 30 milligrams of free ara-C into the lateral ventricle. This is ventricular injection, ventricular sampling. Following the injection of 30 milligrams of free drug, there is a very rapid loss of drug. Half-life is 3.4 hours, and the drug concentration drops below reasonably cytotoxic levels in something less than 36 hours. In contrast, when you inject 50 milligrams of DepoCyt you get a well-behaved two compartment pharmacokinetic curve. This initial distribution phase reflects the spreading out of the particles throughout the CSF, and the elimination phase reflects the slow release of the drug from the CSF compartment.

You will note that we are able to maintain cytotoxic concentrations well out to 14 days and possibly longer with a single injection of DepoCyt, and one can anticipate that when one injects this drug on an every other week dose schedule that there is essentially continuous exposure of the CSF to a cytotoxically effective concentration of drug.

Now, lymphomatous meningitis is a devastating and life-threatening complication of lymphoma. Its frequency has been relatively well-defined in prospective studies from the Southwest Oncology Group of about 3.7 percent, and the signs and symptoms are related to damage to the brain, spinal cord, and nerve roots. Common findings at the time of diagnosis include cranial nerve palsies, paresthesias, focal muscle weakness, headache, neck and back pain, and in severe cases encephalopathy. The progression of the disease is most accurately reflected by worsening of neurologic deficits and the development of new neurologic findings.

This disease is almost always incurable, and there are very few long-term survivors. So palliation is the goal of therapy. Most patients also have active systemic lymphoma, and control of the meningeal disease is necessary but not sufficient for long-term survival. A minority of patients die exclusively of their meningeal disease. So even if you get complete control of this component of the disease, it may not impact on overall survival. The neurologic progression is particularly devastating, often involving loss of vision, hearing, motor function, and bladder and bowel control. It is just a lousy way to die. The standard therapy for this disease consists of radiation to sites of visible disease -- that is, any visible disease you can see on scans -- and intrathecal administration of

ara-C or methotrexate, usually two or even three times per week. Where compatible with planned systemic therapy, some centers use high dose IV ara-C or methotrexate, as well.

Clinical decisions about when to start and stop drugs are largely based on whether or not the CSF is cleared of malignant cells and changes in the neurologic status. CSF neurologic response is de facto the primary decision-making tool used by clinicians in the clinic, and all prior trials of treatment for neoplastic meningitis have included CSF cytologic response as an endpoint.

Now we have a number of problems with the currently available therapy. First, the dose schedule of two to three injections per week is not pharmacologically optimal. Ara-C concentration falls below cytoxic level in less than 36 hours after an injection. We would like to give more frequent IT injections, and they are desirable, but this requires more lumbar punctures and more Ommaya reservoir penetrations. The need to get injections two to three times a week really negatively impacts on the well-being of the patient and the ability of the physician to provide treatment, as you heard in Roxine Reade's case.

Ara-C is important in this disease. Ara-C clearly has activity based on the wide range of clinical experience of physicians throughout the country, and activity is certainly expected based on its effectiveness against

systemic lymphoma when given intravenously. This is why, despite the very small literature on the use of single agent ara-C for lymphomatous meningitis, the FDA agreed that it should be the reference drug in the DepoCyt study.

There are, however, no controlled trials of any form of therapy for this disease. No trials have even included a reference arm. There are no prospective phase 2 trials of any drug in which all patients were treated and evaluated in the same way. There are three small prospective series that have reported single agent activity of 7 and 12 and 4 and 4 in non-Hodgkins lymphoma, and 15 and 15 in African Burkitt's lymphoma, which is a somewhat different kind of disease.

Now, despite the activity of ara-C, the results of current treatment are not good. Even with the use of Ommaya reservoirs, the schedule is not pharmacologically optimal. Median survival is only 1 to 4 months in most series, and shorter for AIDS-related non-Hodgkins lymphoma. Neurologic deficits are usually fixed, and few patients treated with standard therapy have neurologic improvement. If you go around the country asking physicians, you will get a lot of anecdotes about patients that they knew who improved, but there is very little hard data that neurologic deficits present at the time of diagnosis improved. There is a clear need, however, for a more effective therapy that is easier

to administer.

Now we have a number of problems in trying to design and execute trials in this disease. First, there are insufficient numbers of patients to do fully-powered randomized trials. Second, each subtype of neoplastic meningitis has a different natural history, and therefore stratification by subtype is necessary, which increases the number of patients required in randomized trials even further. The commonly used endpoint of decrease in tumor size is not available, because we have no tools to accurately quantitate the extent of tumor burden in the meninges and in the CSF fluid.

The endpoint of survival is difficult to interpret, because these patients by and large are not dying of their meningeal disease; they are dying of their systemic disease. The effects of intrathecal therapy may be confounded by the need to administer systemic chemotherapy at the same time.

We met with the FDA in October of 1992 to work out the development plan for DepoCyt development, and with their advice we designed three randomized trials of the same design, one for each subtype of neoplastic meningitis, and at their recommendation settled on 20 patients per arm in each trial. The purpose of the reference arm was to provide data on a cohort of patients treated at the same centers

over the same time period with comparable supportive care. It was not to provide a group of patients against which statistical tests could be performed. Only one study was to be required for NDA approval for each subtype of disease.

The primary endpoints were response rate, time to response, duration of response, and time to clinical progression, by which we mean in this disease time to neurologic progression, since it is neurologic progression which most accurately reflects the activity of the meningeal component of the disease.

Secondary endpoints were changes in preexisting neurologic signs or symptoms, quality of life, and overall survival. The comparator drug for the lymphoma trial was to be ara-C in its free form and blinded central pathology review was planned, with the analyses of the trial to be based on the diagnosis of the blinded cytologist for all slides that were possible to review.

Patients in both arms of the study would receive oral dexamethasone for days 1 through 5 of each 2-week cycle, and we had a long discussion about MRI and CT scans, and in the end these were rejected as a basis for assessing either response or progression, due to the small fraction of patients with visible disease to start with, insufficient sensitivity, and lack of validation that these tools could be used in this way. I would note that this remains a

controversy today.

The results to be reported were simply the response rate and its confidence interval for each arm, and the studies were clearly not powered to detect statistically significant differences unless these differences were very large. The FDA specified that no statistically significant differences would be required; however, in accordance with good trial design, a prospective statistical plan was included in the protocol.

Now, the anticipated major advantage of DepoCyt when we started this project, by everybody involved, was the more patient-friendly dose schedule. DepoCyt can be given just once every 2 weeks because it maintains cytotoxic concentrations in the CSF for such a prolonged period of time, and thus it requires only one-fourth to one-sixth as many IT injections as standard therapy. This may have the effect of reducing patient suffering associated with lumbar injections or Ommaya injections, reduce the risk of local Ommaya infection, bacterial meningitis, and CSF leakage, all of which are related to the number of Ommaya penetrations.

Also, we anticipated that the dose schedule would be beneficial from a quality of life point of view. The reduced number of physician visits required we anticipated to be particularly important for this very sick population of patients, with neurologic deficits that often impair

their mobility. Finally, it is simply easier to manage the emotional turmoil and functional disruption of the disease when you have a 2-week break between doses, as you heard Roxine comment.

Now the anticipated basis for approval when we started this project was that if the response rates were approximately equal and there were no major differences in toxicity, approval would be based on the advantage of the every 2 weeks schedule.

What did we think we were doing at this point? We thought we were taking an established drug and simply reformulating it into a slow release formulation. When you do this, you normally do this small volunteer study to document that the drug is no worse when reformulated. Now, we cannot do that with DepoCyt, because we cannot give DepoCyt to normal volunteers. We had to do it in a cancer population. However, because the literature base was so small, we and the FDA felt that it was reasonable to include a reference arm to provide a concurrently treated group of patients.

That is what we thought we were doing when we got into this project. We did not anticipate how many years it would take to complete this, nor did we anticipate the changes in the view of how this trial should be evaluated that have occurred over the years.

Now we have completed a number of studies. The phase 1 trial done at the UCSD Cancer Center included six patients with lymphomatous meningitis, and here are the three randomized phase 2 trials, from which is currently available on some patients. We will be focusing on the lymphomatous meningitis trial, which has accrued 33 patients to data. The solid tumor trial accrued 61 patients, and when its accrual was complete, we opened a phase 4 trial in solid tumor patients from which data on 30 patients is available. We have five patients in the phase 2 leukemia trial, and we have conducted a confirmatory pharmacokinetics study. Two other trials we do not yet have data available from; a European PK study and a phase 1 pediatric trial are currently under way.

The total safety database I will be talking about is based on 105 patients treated with this drug so far.

This is the schematic for the lymphoma trial. Patients with positive CSF cytology were randomized to DepoCyt once every 2 weeks for a total of two 2-week cycles or 1 month of induction. Patients on the ara-C were randomized to receive free ara-C at the same dose given twice a week for the same one month period of induction. If the patient had responded by the end of induction, then they were candidates to go on to a consolidation period lasting 3 months, and if they remained in remission at that point,

they could receive a maintenance phase of 4 additional months. I would note that the dosing ratio remains constant throughout. That is, it is always four doses of ara-C to one dose of DepoCyt in all of the phases.

The patients were evaluated for response only at the end of each cycle. That is, the case report forms allowed assessment and captured the data on response only at the same points in both arms of the study. Patients on both arms of the study received po dexamethasone days 1 through 5 of each cycle.

Now I want to be sure that everyone understands what we mean by a cycle of therapy in this study. Cycle was defined on the basis of the DepoCyt dosing interval, and a 2-week cycle consisted of one dose of DepoCyt or four doses of ara-C. So during the induction phase, which consisted of two cycles of treatment, the patient would receive two doses of DepoCyt or a total of eight doses of ara-C.

Now the FDA has raised the question of whether, since some of these patients received dosing outside the time when they were receiving day 1 through 5 dexamethasone, that one would then have uncovered ara-C treatment, but I would point out that when you give a single dose of DepoCyt, this drug stays in the CSF for very long periods of time, and total drug exposure continues way beyond the day 1 through 5 dexamethasone, and in fact, if one wants to

calculate days uncovered by dexamethasone, they are far greater from this kind of a schematic in the DepoCyt arm than they are in the ara-C arm, because following an injection of ara-C the drug disappears from the CSF so rapidly.

The trial required that the patients have histologically proven lymphoma with a positive CSF cytology, a Karnofsky Performance Score of greater than 50 percent; no prior intrathecal ara-C treatment was allowed, but prior methatrexate and CNS radiation were okay. Concurrent limited field CNS radiation was okay, but not whole brain or total craniospinal radiation, and no concurrent IV high dose methatrexate, ara-C, or thioTEPA was permitted.

This study was opened at 27 centers throughout the United States, including some of our very largest cancer centers -- MD Anderson, Memorial Sloan-Kettering. A total of 15 centers contributed 28 patients over the 4-year period up until March 1, 1998.

This slide shows the accrual rate over the 4 years. It was steady, reflecting -- despite a maximal effort to accrue patients to this study -- that the patients available at even our major cancer centers were not large in number, and this makes sense in terms of the math. There are about 60,000 new cases of lymphoma a year. Even if 10 percent of them developed meningitis, that is only 6,000

cases a year. If 3 percent of them are available for clinical trial, then that is about 180 patients per year at all sites in the country. So it is not surprising that our accrual was slow for this study.

I want to be sure that everybody understands the numbers of patients that are included in the analyses of this trial. By March 1, 1998, we had randomized 14 patients to each arm of the study. One patient on the ara-C arm was unable to receive treatment after randomization because the patient developed leukopenia due to systemic chemotherapy. There are then a total of 14 patients on the DepoCyt arm and 13 on the ara-C arm who actually received drug and who are included in all the analyses that I will present to you this afternoon.

Since March 1, 1998, we have accrued an additional five patients, three on the DepoCyt arm and two on the ara-C arm, and the FDA asked that we update all the databases with respect to response information, but the safety information on these patients has not yet been integrated into the safety analyses, in part because some of these patients are still on study.

So the total patients randomized by September 15 were 17 and 15. Unfortunately, one patient's HMO refused to allow treatment after randomization. So we lost that patient, and the numbers that we will be talking about with

respect to response rates this afternoon are 16 patients who actually received drug on the DepoCyt arm and 15 patients who actually received drug on the ara-C arm.

This is a slide of the baseline characteristics of those prognostic factors that have been reported in the literature to be probably of significance in lymphomatous meningitis, and you can appreciate that the two arms of the study are relatively well-balanced, with respect to these factors. There are a large number of other factors that might be relevant as prognostic factors but for which there is no information in the literature or in other bodies of data, and we have examined all of these for their association to response and found no relationship between any of these and response at all. A full discussion of this is provided in your briefing book, and I would be happy to address it further in the question session if necessary.

This diagram shows the actual distribution of cycles received on the two arms of the study, and I want to be sure we understand what we are looking at. Each patient is represented by a different bar. The length of that bar is the number of cycles that the patient received, and you can see that there is a substantial difference. The induction phase consisted of two cycles of therapy, the consolidation phase an additional four cycles of therapy, and the maintenance phase planned four cycles of therapy, as

well. Only one patient in this study received treatment by a lumbar puncture. Everybody else got their treatment via an Ommaya reservoir, and this analysis includes only those patients accrued up through 3/1/98.

The next slide shows exactly the same figure but now links these to the actual total cycles of drug administered, which were 74 on the DepoCyt arm, or 5.5 median per patient, and 44.5, or a median of 2.5 per patient on the ara-C arm. The median time on study was 80 days for DepoCyt and 36 days for ara-C. Recall that you had to be a responder in order to qualify for going on into the consolidation phase. So if you were not a responder, you did not get to stay on study.

A full 14 of the 14 patients on the DepoCyt arm were able to complete induction and get through that phase, whereas only 7 of the 13 patients on the ara-C arm completed induction. Seven of the fourteen on the DepoCyt arm were able to complete consolidation, whereas only 3 of 13 on the ara-C arm were able to complete induction.

Now in approaching the question of how to assess response in this disease, we have relied on the following medical principles. As a minimum requirement, we felt that cytology must convert from a positive to at least one negative examination and that if both ventricular and lumbar cytologies are known to be positive, both must be shown to

convert to negative on at least one subsequent examination, and the patient should not have neurologic progression at the time the cytologic response is documented. Ideally, conversion should occur within the first few cycles, although if it occurs later it is still reasonable to accept this as evidence of drug effect. Finally, one should strive to further confirm all conversions with additional negative cytologic examinations of whatever sites were positive before treatment.

Based on these medical principles, the definition of response that was prospectively called out in the protocol was that the patient needed to convert from a positive to a negative CSF cytology at all sites that were known to be positive at baseline, and lack of neurologic progression at the time that the negative cytology was documented. Confirmation of response with additional cytologic exams was to be attempted in all patients.

Now the specifics of how response was to be scored -- that is, the windows during which the end of induction cytology was to be gotten or a confirmatory cytology -- were worked out with the FDA when the solid tumor NDA was submitted in April 1997 and were included in the analysis plan for that NDA and accepted by the agency. These rules were very rigorously applied to the analysis of the solid tumor trial without objection from the FDA and with complete

agreement as to the number of responses that occurred. We applied these same rules prospectively in exactly the same way to the lymphoma trial, and when you apply the rules in this way, then of the 16 patients on the DepoCyt arm, there were 11 responses for 69 percent; on the ara-C arm among the 15 patients, there were 2 responses, for a response rate of 13 percent, and this is statistically significant with a p of 0.003.

We had a few patients in the phase 1 and PK studies that had lymphomatous meningitis. When you add these in, there were a total of 24 patients treated with DepoCyt with lymphomatous meningitis, 15 of whom responded, for an overall response rate of 63 percent. So in this small series of studies, the response rate is reasonably consistent.

This is an analysis of time to neurologic progression. At the end of each cycle, the physician was asked to make a global assessment of whether the patient had suffered neurologic progression or not, and the Kaplan-Meier plots for the time to neurologic progression are shown here. There is a trend toward an improvement in the DepoCyt treated patients, with a median of 78.5 days versus 42 days, but this is not statistically significant.

We also had planned to examine time to response and duration of response. However, there are so few

responses in the ara-C arm that we could not get much useful comparative information. Nine of the ten patients on the DepoCyt arm had responded by the end of their first two cycles, as had one patient of the two responders on the ara-C arm, and we could define a median duration of response for the patients on the DepoCyt arm who responded of 38 days, but there were only two responders on the ara-C arm. They had durations of response of 15 and 33 days.

We took two approaches to the analysis of quality of life in these trials. The first was a prospective approach in which we monitored and collected data on three things: the Karnofsky performance status, the FACT-CNS instrument which is a patient questionnaire instrument, and the mini mental status examination which is an abbreviated standard neurologic mental status examination.

Retrospectively we also applied the Q-TWiST analytic technique. That is, we collected all the data on adverse events prospectively, and when the data was available we conducted a Q-TWiST analysis. I am not going to discuss the Q-TWiST analysis today. A full discussion is presented in your briefing book, and I would be happy to entertain questions on it later.

The change in the Karnofsky status, we feel, is the most robust of these instruments in that it is widely accepted as a valid measure of patient performance. Now the

Karnofsky status was determined at baseline and the end of induction, and the number of patients completing induction on the DepoCyt arm was 14. Data is available for 13 patients. Thirty-one percent of those had an improved score, no change had occurred in 54 percent, and only 15 percent had a worsening score.

Of the eight patients who completed induction on the ara-C arm, data is available on all eight, and there was an improved score in 25 percent, no change in only 12 percent, and a worsening of score in a full 63 percent of the patients.

Now the FDA has criticized this analysis on the basis that there is a lot of missing data. However, you note that of the patients who completed the induction phase and therefore could have data available, only one patient is missing out of the 13 patients on the DepoCyt arm and the eight patients on the ara-C arm.

We also looked at the Karnofsky score at the end of induction by subtracting that from the baseline for each patient in a paired within patient analysis and looked at the average change determined for each group. The mean change in score favored DepoCyt, and this difference was statistically significant. I would note that this difference would be a lot larger and more favorable to DepoCyt if the six patients on the ara-C arm who failed to

complete induction were included, because of course their Karnofsky status would be expected to go much further down, and if they died before completing induction, it would be zero.

Now the FDA has criticized this analysis on the basis that we had multiple endpoints that we followed, and of course if you do 20 statistical tests and you use a p of .05, 1 out of this 20 by random chance might be positive, but we are dealing with only three prospectively monitored quality of life issues here. The FACT-CNS and mini mental status exams -- results I am not going to discuss; they are presented in your briefing book -- they are both favorable to DepoCyt. However, our conclusion is that these are not good instruments for following quality of life in these patients, and we do not think the data is terribly useful or meaningful.

This is overall survival. We did not anticipate an impact on overall survival, and we did not see one. There is a median of 99.5 days for DepoCyt versus 63 days on the ara-C arm. The FDA has criticized this analysis by saying that our 6 and 12 month survivals do not match theirs. I would explain that by indicating that our 6 and 12 month survival was determined from a Kaplan-Meier projection of survival, whereas theirs appears to be determined by simply numerically adding up how many patients

were alive at 6 and 12 months.

All measures of efficacy in this study favored DepoCyt. There was a higher response rate of 69 percent versus 13 percent, which was significant. The response rate is consistent with the results of the phase 1 and pharmacokinetics studies. More DepoCyt treated patients were able to complete the planned induction and consolidation phases of therapy, and there was an increase in median time to neurologic progression which was, however, not statistically significant.

The DepoCyt treated patients had an improved quality of life as measured by the robust Karnofsky score measure over the first two cycles of treatment and as measured by the Q-TWiST analysis. The Q-TwiST analysis actually indicated a 5.9-fold increase in time free from toxicity due to treatment or disease progression in favor of DepoCyt.

Now, the FDA has challenged us on these response rates and has changed its criteria on how patients should be scored for response and proposed three alternative scenarios, all of which we believe are somewhat problematic. First, it is scientifically appropriate to have the same rules for recording response in the DepoCyt solid tumor trials and the lymphoma trials. Whatever rules we agree on should be applied equally to both studies.

Notwithstanding this, we think it is possible to reconcile our differences on the data in a way that still support approval of this NDA. For example, we are in complete agreement with the FDA that scenario 3 is not valid, because it would accept as responders patients in whom there is inadequate cytologic follow-up.

With regard to the issue of central cytopathology review, the protocol states that central cytologist's review will be final for purposes of efficacy review. However, there will be some missing slides. In fact, in no oncology trial has it ever been possible to review 100 percent of the slides centrally. So the analytic plan stipulated the use of the local cytologist's reading when the slides could not be recovered for central cytopathology review. This plan was accepted by the FDA at the time of submission of the solid tumor NDA, and exactly the same plan was prospectively applied to the lymphoma trial analysis.

Even if the lack of central pathology review is considered a protocol violation, as has been identified by the FDA, the missing review involves only five critical slides in a total of four patients whose response was based in part on the local cytologist's reading. If you apply the discrepancy rates that were found -- that is, the rates at which one cytologist read it one way and the other cytologist read it the other way -- you would expect at most

a change in the reading on one slide, and therefore we think it is inappropriate to reclassify all four patients who are lacking a central cytopathology review as non-responders, as has been proposed in the FDA scenario number 1.

There are also some factual errors in the FDA's analysis, and I do not think anybody needs to be held responsible for these. We all had to work under a very short timeline, and such factual errors occasionally occur under this situation. There was one patient on the DepoCyt arm who was scored as a responder despite suffering neurologic progression before the end of induction, and this patient, we feel, should not be scored as a responder.

There were also two additional patients who actually meet all of the FDA criteria for response, and those happened to be on the DepoCyt arm.

Now, scenario 1 that the FDA proposes we are concerned about, because it discards all patients lacking central cytopathology review, which we think is an unrealistic standard. No such trial has ever obtained this, and it is standard to include in analytic plans a mechanism for dealing with missing data.

Scenario 2 we are concerned about because it would accept patients with neurologic progressions as responders, at least as the FDA has provided this to you in the briefing book. They may have changed their mind on this. It rejects

all patients with cytologic conversion at all sites known to be positive if they do not have two consecutive negative cytologies, and I will come back to this point and discuss it in more detail in just a moment.

Scenario 3, I think we both agree is not acceptable, because it accepts as responders patients who are clearly unevaluable due to inadequate cytologic documentation.

What we would propose, using the FDA's strategy of scenarios, is scenario 2-plus, which is based on their scenario and is identical except for one point, shown in yellow. We would accept as responders all patients meeting the very strictest interpretation of the protocol. We would also accept as responders patients who had a late primary or confirmatory cytology. We are talking about 1 or a couple of days late. In fact, the longer the patient goes with a negative cytology, the better it is likely to be for that patient.

Third, we would accept patients as responders who did not have a central cytology review, for the reasons that I have just indicated. Finally, we would accept patients who converted by the end of induction but did not have two consecutive negative cytologies, and I will address this in detail in a minute, but we would reject as responders patients who suffered neurologic progression before

completing induction and patients in whom cytologic conversion was not documented at all sites known to be positive at baseline.

Now let me talk about this business of accepting patients as responders who do not have a confirmed negative cytology, and I have shown the situation schematically here. See, here is a patient who has a ventricular positive cytology before treatment. The lumbar sac is also positive. They get a couple of cycles of DepoCyt, and both sites become negative, but we were unable to get a confirmatory cytology.

First of all, I would point out that there are good medical reasons why you might not get confirmatory negative cytology. Remember, a lot of these patients are receiving systemic chemotherapy at the same time, and when your patient is thrombocytopenic, you cannot do a lumbar puncture. So there are a group of patients in the database that fit this category.

First of all, spontaneous clearing of the CSF is not known to occur in this disease. Secondly, FDA accepted such patients as responders in the solid tumor trial, where it worked somewhat against DepoCyt. Third, the CSF sampling error that certainly one would be concerned about here is probably lower in lymphomatous meningitis than it is in solid tumors, and there really is no information available

about CSF sampling error in a patient who you already know has a positive cytology. All the literature information relates to patients in whom you are trying to make the diagnosis in the first place.

So we think that this kind of situation does in fact reflect some evidence of drug activity and propose that these patients be considered responders as we look at this data.

If you simply correct the factual errors in the FDA's analysis and look at the response rates that one gets then with scenarios 1, 2, and 2-plus, you get the following. If you take the very strictest interpretation of the protocol, that is 4 versus 1, and I would note here that the FDA in doing its analysis now has added back into the ITT population the two patients, one on each arm, who never received drug. If you look at scenario 2, it is 8 versus 1, 8 of 17 versus 1 of 16, and if you accept our scenario 2-plus situation, it is 11 out of 16. You will note that this is exactly the number that we came up with using the rules that were prospectively defined in the original analysis plan -- I am sorry, it was defined in the analysis plan and prospectively applied to this particular study.

I would note that no matter how you cut the data, the response rate for DepoCyt is higher, and this is consistent with the fact that you maintain cytotoxic

concentrations of drug in the CSF for very long periods of time with DepoCyt in comparison to ara-C.

All right, let's turn to the safety analysis of DepoCyt. The safety analysis is fundamentally different from what was presented to you in December of 1997. The prior approach was based on analysis of adverse events per patient, and this was confounded by the fact that DepoCyt-treated patients responded better and therefore remained on study longer and received more cycles.

The current approach is based on an analysis of adverse events per cycle. So the number of patients reporting adverse events in cycle 1 of DepoCyt is compared to those reporting events in cycle 1 of ara-C, and the same for cycle 2 and so forth. This approach is appropriate because the adverse events were largely transient and had resolved by the end of the cycle and is in fact based on the recommendations that were made when you all discussed this drug last time.

The safety of DepoCyt has been assessed using the data from all 105 patients treated as of March 1, 1998, and the full analysis is presented in your briefing book. I am going to discuss only the highlights in my presentation.

Headache was the only adverse event that occurred in more than 10 percent of the cycles in any trial, and headache is included in the symptom complex of

arachnoiditis, and arachnoiditis was the only medically important event that was observed in these studies. A significant fraction of these patients had disease-related arachnoiditis prior to study entry, and it was often difficult to distinguish between arachnoiditis present prior to study entry and arachnoiditis related to drug following the onset of treatment.

The headache occurred across all studies relatively infrequently. Headache of any grade occurred on 25 percent of cycles but was grade 3 on only 5 percent, and recall that a grade 1 headache is a mild headache, a grade 2 is a moderate or severe headache which is transient, and a grade 3 headache is a moderate or severe headache which is more persistent.

In fact, when it occurred, 78 percent of all the episodes of headache were just grade 1 or grade 2, and when they occurred as an isolated episode, they were transient, median less than 1 day of duration. This headache was easily managed with aspirin or acetaminophen, and in fact, analgesia use, either opioid or non-opioid analgesia use, was very well balanced in the two arms of the study.

Headache often occurred as part of an episode of arachnoiditis. In fact, 56 percent of all episodes of any grade of headache occurred as part of an episode of arachnoiditis.

This is the depiction of headache in the two arms of the lymphoma study, and let me make sure that everyone understands what this histogram shows. The height of the bar is the number of patients treated in that cycle. The pink area is the number of patients who had no headache associated with that cycle, the yellow area the number of patients with grade 1 or grade 2 headache, and the blue area the number of patients with a grade 3 headache. Shown for comparative purposes only are the headaches that were present at study entry in both of the two arms. One can appreciate that there is a slight difference in the incidence of headache between the two arms and that there are a few more episodes of grade 3 headache on the DepoCyt arm, entirely consistent with the fact that we are maintaining high concentrations of drug in the CSF of these patients for much longer periods of time and producing a much larger tumor effect as evidenced by the response rate.

The difference in headache frequency in the solid tumor trial between DepoCyt and methotrexate is very much less impressive. A lot more of these patients on the solid tumor trial had headache at the time they entered the study, and in fact the frequency went down with each additional cycle of treatment.

Finally, in the phase 4 trial, the 30 patients who are now available from the phase 4 trial, the overall

incidence of headache is substantially less, and this appears to reflect the greater experience of physicians with the drug and the more consistent use of dexamethasone as per protocol.

This plot shows every patient on the DepoCyt arm of the lymphoma trial. Each bar represents a separate patient. The duration and the length of the bar represents the duration on study, and the white area indicates no grade 3 headache. This shows only the grade 3 headaches, and there were one, two, three, four patients who experienced a grade 3 headache at any time on study and, in fact, out of the whole group of 14, six patients had no headache of any grade at any time on study. So the duration of time on study burdened by a serious degree of headache is very, very small indeed.

I am going to step out to a backup slide to address a point made by the FDA here, and that has to do with the dexamethasone usage in this study. I would point out that the percent of time on study with dexamethasone is very, very well-balanced between the two arms. This is the actual number of days that patients on study received steroids, and it is 48 percent of the days for DepoCyt and 51 percent of the days for ara-C.

Now, arachnoiditis is of concern whenever you are giving drugs intrathecally, and it can be caused both by

tumor infiltration of the meninges and by intrathecal administration of drugs, and it is often difficult to distinguish between these two. Scoring for arachnoiditis in these trials was based on a standardized algorithm, because the criteria for making the clinical diagnosis of arachnoiditis varied so much between different physicians at different institutions.

So the algorithm is as follows: patients were scored as having drug-related arachnoiditis if within 4 days of drug injection they developed either neck rigidity, neck pain, or meningismus, or any two of nausea, vomiting, headache, fever, back pain, or CSF pleocytosis. The arachnoiditis was graded on the basis of the highest grade of any of the constellation of adverse events. So if you had a grade 2 vomiting and that was the highest grade of any of the elements, you had a grade 2 arachnoiditis, and I want to point out, as also mentioned by the FDA, that this is a very conservative approach that may overestimate the true frequency of arachnoiditis, because if within 4 days of drug injection you had some vomiting and a headache, you got scored as having arachnoiditis. However, this is the reason that we have broken out individually each of the components that went into the diagnosis of arachnoiditis, as well, and presented them in your briefing book.

If you look at arachnoiditis across all studies,

including arachnoiditis whether or not it was thought to be drug-related, it occurred on 19 percent of cycles on the DepoCyt arms of the studies and on 5 percent of the cycles was it grade 3. Of all the episodes that occurred, 71 percent of all episodes were just grade 1 or grade 2, and there was no meaningful difference in the incidence between DepoCyt, ara-C, or methatrexate, and I will show you that in a moment.

When it occurred, the arachnoiditis was transient and resolved over several days. In all episodes it resolved before drug treatment was due 2 weeks later, and it did not prevent on-schedule treatment with additional cycles of drug. In fact, no patient went off study because of arachnoiditis in the lymphoma trial.

This is the comparison of the actual rates for each of the drugs across all studies. Arachnoiditis occurred on 22 percent of the cycles in the lymphoma study for DepoCyt and on 13 percent of the ara-C cycles in the lymphoma. It occurred on 23 versus 19 percent of cycles for DepoCyt versus methatrexate on the solid tumor trial, and in the phase 4 trial it occurred on 15 percent of cycles. But if you look at just the serious arachnoiditis, it is 8, 7, 4, 3, 4 -- essentially no differences in the incidence of serious arachnoiditis between these different drugs.

If you ask how many patients who developed an

episode of arachnoiditis went on to stay on study and receive additional DepoCyt treatments, 7 of the 9 patients on the DepoCyt arm who developed arachnoiditis continued on study. None of them went off because of arachnoiditis, and 5 of the 6 patients on the ara-C arm who developed arachnoiditis stayed on study. None of them went off because of arachnoiditis. In fact, the number of additional cycles that these patients received is listed here, and it is quite a large number of additional cycles. So arachnoiditis did not cause a serious enough problem that the patient could not stay on study and continue to receive intrathecal treatment.

Now the FDA has noted in its question to you -- one of its questions to you -- that there were 11 patients on the DepoCyt arm of the solid tumor trial that were hospitalized with symptoms suggestive of arachnoiditis, compared to two on the methotrexate arm of the solid tumor trial. I would like to point out that this is an erroneous statement. This quote was taken from the integrated study report and not from the methatrexate versus DepoCyt solid tumor trial. So, in fact, only 4 of these 11 patients are on the solid tumor DepoCyt trial. Most of the rest of them are on the pharmacokinetics study and the phase 1 trial. So this is an incorrect statement, and in fact, hospitalizations in the lymphoma trial in the two arms were

equally balanced across both arms, and when hospitalization occurred it was not necessarily because of arachnoiditis. Often these patients were hospitalized for a variety of other reasons -- for example, to receive intravenous chemotherapy -- and happened within 4 days of dosing with DepoCyt to have a headache and some nausea. That qualified them as having symptoms associated with arachnoiditis.

In the lymphoma controlled trial, there was only one patient hospitalized on the DepoCyt arm with symptoms that could be related to arachnoiditis, and again, it is not because of arachnoiditis.

The FDA has raised an issue about four cases of neutropenia, and let me show you where these came from. These were all grade 4 cases, and they were considered by the treating physician to be only possibly related to DepoCyt therapy. The first of these received radiation therapy immediately before receiving DepoCyt and had a nadir on day 18. The second had DDP, IDA, high dose ara-C before study, and this patient by the way is a protocol violation, and is not included in any of the calculations, but just to show you where the granulocytopenia came from. That patient developed neutropenia on day 20. The third patient, on cytophosphilide(?) doxin(?) developed the nadir on day 11, and the fourth patient, cytophospholide dox, VP-16, AIDS-related patient receiving fairly large doses, had a nadir on

day 11. All cases occurred at the expected times after the systemic chemotherapy or radiation, and the concept that DepoCyt would be contributing to this grade 4 neutropenia is simply inconsistent with the well-known pharmacology of this drug and the concentrations which were produced in the systemic circulation, which are essentially non-measurable.

The FDA has also raised a question about whether one death that occurred on study might possibly have been related to the drug. This was a 63-year-old male with a primary large cell testicular lymphoma presented in January of 1992 with a history of aortic aneurysm, cardiomyopathy, a recent duodenal ulcer, and congestive heart failure. The patient had extensive ocular and nasopharyngeal involvement, as well as the neoplastic meningitis at study entry. He was dosed on December 6 and December 20, and 2 days later, after his second dose, complained of severe neck and pain but had a completely normal neurologic examination.

The patient died at home 4 days later unattended, and the death was attributed by the physician to the progression of lymphoma, but appropriately the physician scored this as possibly related to DepoCyt, because information was lacking as to the patient's death. That patient was cared for by Dr. William Shapiro who is here with us today, and I am sure he would be pleased to comment on it further if it is an issue.

So overall, regarding the safety conclusions for DepoCyt, the only toxicities of medical significance were headache and arachnoiditis. The DepoCyt toxicities were qualitatively similar to those of ara-C and methatrexate, and no toxicities unique to DepoCyt were identified. The toxicities were generally mild, transient, well-tolerated and easily managed, and there was no evidence of cumulative toxicity of any type in any of the studies that we have accomplished so far.

Now, with regard to whether this drug should be approved at this time or not, I would like to point out that this is the only prospective randomized controlled trial ever conducted in lymphomatous meningitis and that it is very likely that such a trial can ever be repeated. First, it is a rare disease. It requires a lot of sites and a long period of time and a lot of resources that nobody is willing to put in any more. Any new trial will also face the same scientific issues of inability to get 100 percent central cytology review and missing data that this trial is plagued by.

DepoCyt is not a new chemical entity. It is an old established drug that is a novel formulation of this drug, and this novel formulation achieves a pharmacokinetic profile in the CSF that has long been sought. The pharmacologic rationale for long-duration exposure is well-

founded. The toxicity of ara-C is well understood, and there is an enormous body of clinical experience with the intrathecal administration of free ara-C.

DepoCyt produced the results that can be reasonably expected of an agent that controls the meningeal component of the disease. It produced a high CSF response rate, no matter how you cut the data, and some evidence for an increase in time to neurologic progression. The risk of making DepoCyt available commercially is low. This drug would be used in a small number of patients cared for by specialists with specific expertise in the use of ara-C, and DepoCyt provides a badly needed additional treatment option for patients with a devastating disease such as you heard requested by Roxine Reade.

Now the FDA will ask you to address the question of whether DepoCyt provides a meaningful advantage over existing treatment, and they have couched this question in terms of response rate. I would urge you also to consider the advantage of the once every 2 week dose schedule, which has the potential to reduce patient suffering associated with the injections, reduce the local Ommaya infection rate, bacterial meningitis, and CSF leakage problems, reduce the number of visits to a physician, and just make it easier to tolerate treatment. This was where we started with this drug, and we believe that it is an extremely important piece

of the advantage that DepoCyt affords.

The FDA will ask you whether this is an adequate and well-controlled trial for assessing response. Well, DepoCyt does produce response rates in lymphomatous meningitis, and in all the scenarios, DepoCyt produces a higher response rate than ara-C. I remind you that any new trial, by virtue of the clinical complexity of these cases, will also yield incomplete data and face exactly the same problems that we face in evaluating this trial today.

Now, should you be inclined to support approval, you will not be alone. A number of your colleagues have reviewed exactly the same data that you have seen here today and have voiced their strong support for making this drug available so that all of us can address and answer the questions that we want to know about how best to use this drug. How long should we treat? Can we reduce the arachnoiditis rate if we give intrathecal steroids along with the drug, and so forth.

I would point out that your assessment today is critical to the future of this drug. As many of you may know, DepoCyt has run out of money and will go out of business. The company is trying to execute a merger and a transfer of its technology to another partner, but the level of enthusiasm that you express here today will in large part and in all probability determine whether any further studies

of this drug are undertaken.

Let me leave you with an overall summary of where we stand. We think this drug produces a higher response rate. In our original rules of analysis, this yielded 69 versus 13 percent. The FDA's scenario 2 yields 41 versus 6 percent; our proposed 2-plus yields 65 versus 12. A high response rate is reasonably likely to predict clinical benefit in this disease. More DepoCyt patients were able to complete the planned induction and consolidation phases of treatment, and there was a trend toward an increase in median time to progression.

Important again is this more patient-friendly dose schedule and the fact that there is some evidence for an improved quality of life based on a robust well-accepted measure. Finally, the safety of DepoCyt is acceptable, given the life-threatening nature of the disease and the benefit afforded by the drug, and this can be attested to by our investigators who accompanied me today who have direct experience with the drug.

Thank you ever so much.

DR. DUTCHER: Thank you very much. Are there questions from the committee for the sponsor?

DR. WILLIAMS: Dr. Howell, I just want to clarify a few statements that you made. First of all, there were numerous statements about what the FDA said or what the FDA

did wrong here that I think are not correct. So we did have a meeting about 2 weeks ago, a telecon, at which we specifically discussed each patient's individual data. We did not discuss interpretations at the time, but we did present our views and let you know on each specific piece of data what we thought the ramifications would be if you accepted it.

Of your numerous statements, I only want to address a few. Helgi will be presenting our analysis, and any of the analyses we see here I do not accept as being FDA scenarios unless it is from us. In terms of the patient with neurologic progression on slide 56, as we faxed to you Friday, we did look at the neurologic progression data, and we accepted the investigator's response which reflects the global, which you have used in all your other neurologic analyses. We did not accept your reassessment of that neurologic progression. That is why we left that patient in ara-C as a responder, because subsequently he did okay.

In terms of what we hear about the analysis plan, which initially you had told us was the protocol-specified analysis for endpoints such as response, this plan was not agreed upon by the FDA. It certainly was not at the time the NDA was submitted. We did not say we agree with your analysis plan.

I will probably leave Helgi to present our

different analyses, but we know exactly what you think on every analysis on every patient. We have our opinions and our criteria, and we stick by them. It is not that we have made errors, as you stated. So we will leave Helgi to present our analyses, but I did want to specifically address that the statements you have made against us I do not believe are true.

DR. HOWELL: I guess there was a question in there somewhere, but let me just say again that we all worked, as you did, very, very rapidly, and I think you all and our team did a remarkable job under a very, very short deadline. So let me reiterate to everybody that I appreciate the effort that the FDA has made, and if a few errors have crept in here, I want to be sure that you do not feel that I am blaming anybody on these.

I think there are a couple of errors. We will stick by our guns as well, but the bottom line is I think we could come to a reasonable agreement about what the response rates are, and I think it is worth an effort to try to do that.

DR. WILLIAMS: We have looked at what you think are errors, and we do not think there are errors. I just did not want the committee to think that there is any doubt in our mind about what we think the data are.

DR. DUTCHER: Dr. Schilsky?

DR. SCHILSKY: Steve, a few questions. You know, I think we would all agree that a primary goal in treating patients with neoplastic meningitis is to prevent neurological progression or, in the best of all possible worlds, to improve neurological deficits and to do that with an acceptable level of toxicity. So I am a little bit struck by all of the information that is in the briefing books from both parties, as well as your presentation, by the intense focus on cytologic response, and almost complete lack of discussion of anything about how the patients are doing clinically, because in my mind, while it is nice to see cytologies become negative, that is really not the primary focus of treating these patients who have a short survival no matter what you do, and as you point out, oftentimes die from uncontrolled systemic disease. So what you really want to try to do is to keep them alive as long as you can with as little neurological deficit as possible.

So can you tell us something about things like what were the neurological deficits that were observed in these patients at the time that they entered the study? It would also be useful to know exactly how was neurologic progression defined in the protocol? No one has told us anything about under what circumstances was a patient considered to be neurologically worse. Maybe I will just start with those two questions.

DR. HOWELL: All right, let me answer them in reversed order. First of all, at the end of each cycle of therapy, the physician was asked to record a neurologic examination, and as a separate item make a global assessment of the overall -- whether or not that patient was suffering progression or not. So there were two pieces of data that are captured by the case report forms.

All of the analyses of time to neurologic progression are based on the physician's global assessment of the patient's status. Now the actual neurologic examinations themselves were analyzed to ask what can we find out about how these patients improved, and this data is shown on the next backup slide.

We asked the question what fraction of patients had improvement in the neurologic deficits present at study entry. The bottom line is that we do not think a credible determination based on the individual elements of the neurologic exam can be made, for the following reasons. These changes were often very transient. Improvements in one deficit often were accompanied by worsening of another deficit. So it left you in a quandary as to whether to score this patient as improving or not. Many changes such as general muscle weakness were related to systemic disease and treatment rather than to the meningeal disease, and it was often not possible to clearly distinguish between these.

Now I can show you a very complicated slide looking at whether there was a change in every element of the neurologic examination, but it is not believable. It is not credible. So our conclusion from the analysis of the neurologic exams was that a lot of these things are changing in transient ways that do not allow us to answer this question in a believable and cogent way.

Separate from that, we believe we can make a believable and cogent analysis of time to neurologic progression, which is based on the physician's overall assessment of the patient with all the information factored into the situation.

DR. SCHILSKY: That suggests to me, though, that the individual physicians might interpret neurological progression in a variety of different ways, and certainly I would agree that some neurologic deficits might improve while others worsen. Were there guidelines provided in the protocol with respect to how neurologic change in the patient should be interpreted? Was it left entirely to the discretion of the treating physician? How are we supposed to get at --

DR. HOWELL: There were detailed elements of the case report form for the recording of the neurologic examinations. There was no specific guidance given to the physician regarding their overall assessment of neurologic

progression, and perhaps I can call on Dr. William Shapiro to address that issue more cogently, since he is an expert in this specific field.

DR. SHAPIRO: You know, the problem is that patients with meningeal tumor are late in their course, and their illness is devastating in the sense that it goes from a private illness to a public one. A patient who has an enlarged liver or a big spleen, maybe even having pain in a joint, is not so obvious to anybody else, but when that patient becomes peripatetic or begins throwing up or develops dyplopia, it is a whole new problem for him. These patients come to us as neurooncologists because of the neurological problems.

The great bulk of these patients do not get a whole lot better. The best we can get from treatment is that we slow things down a bit, and therefore it is easier to see worsening than it is to see improvement, and that is clearly what we are talking about.

Going back almost 25 years when I began in this and wrote the first paper on the distribution of methatrexate in these patients, it was very apparent that meningeal lymphoma was the best of the tumors that could be treated, and something like 60 percent of patients got better in the sense that they did not get worse.

We used cytologic conversion from the very

beginning, and in fact, you did not change the dosing of your drug unless you got cytologic improvement. Since you were using a drug twice a week, this was a very important issue. So you would use it twice a week, you would wait 1 month, you would do a CSF cytology. If it improved, which meant getting a negative conversion, then you quit using the drug twice a week. You would go to once a week and then once every 2 weeks and then once a month. One of the nice things about DepoCyt was that you did not have to do it twice a week from the very beginning.

So I think the answer to your question is some things improved, mostly subjective things. They quit throwing up, the headaches went away, they felt better -- hence, the sense of global overall neurological function. But peripatetic patients rarely got up and walked. There is just no question about it. Frequently, they got continent, and that is a big change. I mean, lying in your own stool and feces is not a pleasant experience. But they did not get a whole lot better. Mostly they just did not get worse.

DR. SCHILSKY: [Question off-mike.]

DR. SHAPIRO: Well, those are not exclusive. I mean, I took care of patients in this trial the same way I took care of patients everywhere else. We helped write the protocol. The neurologic examination which was depicted there was the one that we helped to write.

DR. SCHILSKY: But we are being asked to evaluate this particular clinical trial.

DR. SHAPIRO: I understand. We wrote down what happened to the patients. In addition, we all agreed that since it was unlikely that the neurological exam would get better, we had to give him an opinion from the trenches about what we thought was going on in the patients with whatever the treatment was, and that the beginning we did not know whether this was going to work. Hence the global.

DR. SCHILSKY: Steve, let me ask the question in a slightly different way, because I notice that in some of the data that you presented at the beginning of your presentation, that after the induction cycles of chemotherapy, approximately half of the patients on the ara-C arm, the free ara-C arm, were scored as non-responders. Now, to be a non-responder at that point would require either that you have a persistently positive cytology or that you have neurological progression. So how many fell into those two categories?

DR. HOWELL: Or that you died in the process.

DR. SCHILSKY: Yes. So of the seven or eight patients who were non-responders after two cycles of ara-C, how many were non-responders because of neurologic progression or death as opposed to just persistently positive cytology? That at least gives us sort of a

background or perspective to put the DepoCyt data in.

DR. HOWELL: Let's look at what happened to those patients who failed to complete their induction. This is the same diagram that you have seen before. So this is time on study, number of cycles. So here are the patients on the ara-C arm who failed to complete induction. One had a progression of lymphomatous meningitis, another had an adverse event related to their disease, another died of a systemic progression of disease. One patient here, the physician felt it was not in the patient's best interest to continue therapy, because nothing seemed to be happening, and the day 15 cytology remained positive. Another death due to systemic progression, and another physician who felt that the patient was not doing very well and needed to go on to some non-study drug. So those are the reasons those patients did not complete.

One can interpret those as fairly strongly related to failure to control the meningeal disease, but not all of the cases were just failure to control the meningeal disease. However, they are pretty well balanced in the two arms. Those patients who died early in the DepoCyt arm also died of systemic disease and a couple even died of the meningeal disease.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: Well, actually, the only reason I

wanted to pipe in here is because I had a related question that since it seems like we have gone back and forth with what the FDA is going to say, the importance of the concomitant therapy as well as prior therapy, but most importantly concomitant therapy, radiation therapy to small fields, and most importantly systemic therapy, and then other disease features such as how many relapses the patients had had and the types of lymphoma histologies were not mentioned in any of your presentations. They seemed to be imbalanced in the briefing documents. So if you could comment on that.

DR. HOWELL: Sure. You can make up a list of about 20 things that you think might impact on patients' prognosis with this disease. Let's go to 109. The full list of that is provided in your briefing book, and there are some imbalances. You expect some imbalances of any one factor that you are going to look at in small studies like this. With a larger study, these would unwind and there would be fewer things.

Here is the status of the systemic disease. In the back somewhere in the briefing book we do have a list of all the histologies that were available to us. Some of these patients came through neurooncologists, and we were not able to recover the histology of the original lymphoma, but they are not different between the two study arms.

Let me just comment and show you the problem that we face, and I think all of us face in trying to deal with slight -- you know, with some unbalances when you have a number of things. The next slide shows that there are even more things that one could look at to ask what is balanced and what is not, and here in fact is the histologic subtype of the lymphomas for you.

Let's just take the case of concurrent systemic chemotherapy. Now which way does that bias the situation? More of the DepoCyt patients received concurrent chemotherapy. Now does that mean that they had worse disease and things were going worse for them and we should accept that as a negative and say these patients were then anticipated to do worse, or does it mean that, gee, maybe some of the systemically administered drug leaks back into the CSF and contributes to the meningeal response. The answer is I don't know, and I cannot sort it out from this database, right? And we are stuck with exactly that problem with a number of these other imbalances that they cut both ways, and in the absence of definitive information of any type, I cannot tell you.

What I can tell you is that when we looked for an association between any of these factors and response, we did not find it. So we were unable to link any of these factors to response. It is a small study, and you would

like to have a lot more numbers when you do that kind of analysis.

DR. SCHILSKY: Steve, another place where that issue of concurrent systemic chemotherapy could have an impact is on assessment of performance status, which you have argued is perhaps the most robust way of evaluating quality of life impact of the therapy. There were twice as many patients on the DepoCyt arm getting systemic chemotherapy, and we do not know at this point anything about whether they responded to that therapy or not, but since the Karnofsky performance status rating for those patients would reflect not only the impact of their lymphomatous meningitis but would also reflect the impact of their systemic lymphoma, it is conceivable that some of the improvement in performance status that the patients on the DepoCyt arm had might have been due to response to systemic chemotherapy which allowed their performance --

DR. HOWELL: It might, but most patients getting systemic chemotherapy -- and remember that more of the patients on the DepoCyt arm got it -- have a worse Karnofsky performance status simply because they are getting the therapy. I mean, standard job therapy impacts on the patient's well-being as reflected by Karnofsky.

I do not disagree with your argument. The bottom line is the numbers are just too small to be able to

definitively answer your question, but again, I think one could interpret the data in both directions, and I do not have a good way to answer that question.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: Back to the issue about some general aspects of the study design and your repeated statements that it would be impossible to do this sort of a trial in the future or a trial that would make up for some of the apparent deficiencies here, it is bothersome to see that this trial is very tiny. You had quite a large number of centers. Only 30 or a few more than 30 patients, but still unable to get nearly complete central pathology review, and all of the pieces of data that were anticipated initially and were required by FDA, with a very loose statistical plan entailing only comparable outcomes and comparable toxicities. I do not understand why a trial cannot be designed that is larger that accrues more patients and that can also control for some of these other variables, which, as you say, have unknown impact on the outcomes, but you have to recognize that they may have some impact and influence how we interpret the data.

DR. HOWELL: Well, I can tell you why this is a small study, even after 4 years of attempting to accrue. First of all, there are not a lot of these patients, and I showed you the math on those. Secondly, many of these

patients have received a dose or two of intrathecal ara-C. They come into the clinic. They get an LP. The physician pops in a dose of ara-C even before the cytology is available, and that patient becomes ineligible for the trial.

Third, a large number of patients do not develop their lymphomatous meningitis until they have already had their disease for a while, and they are usually on an ECOG or a SWOG or a CALGB(?) study which precludes an additional experimental agent. So none of those patients, when they develop their lymphomatous meningitis are candidates for this study.

So that is the operational difficulty in accruing these patients. It is not that there was any lack of effort to accrue these patients, and in fact, I think most lymphoma experts in the country have talked to me at one time or another about participating in this trial. There was a major effort to accrue to this study, and what you are seeing is the clinical reality of this disease.

DR. MARGOLIN: I think all those things are valid, except that I think the last point is a little strange, that patients would be on large cooperative group studies for the primary treatment of their lymphoma and subsequently for a failure defining event not be allowed to go onto some kind of an IND trial, because at that point the patient is

generally off study.

DR. HOWELL: Well, I do not write the cooperative group studies most of you all do.

Let me ask Sandy Horning to talk about that, who is far better and more of an expert in lymphoma than I am.

DR. HORNING: Well, I just wanted to comment that I think that looking at this data set that what we can all agree upon is that the numbers are small, that the patients are very heterogeneous, and that it is frustrating that you cannot come to a cleaner conclusion. But I do not think it should be surprising that that is the case, because one could think of at least six very common scenarios, each of them very different one from another, that in which case one sees CNS lymphomatous meningitis, and if you were really trying to get at the heart of this problem, I think you would need an enormous trial, probably an international effort, that really focused on each of those subset scenarios for the various indications.

The other thing that I think comes into play with this situation is that many patients are in the setting, like the patient that gave the testimonial, and that is that they have had their lymphoma for a number of years, it is now progressing, they are getting concomitant chemotherapy or other treatments, and it may be difficult for them to meet the eligibility criteria that are set up for an

investigational study simply from the hematologic point of view.

DR. HOWELL: Well, yes. We contacted all of the major cancer centers in the United States, and we contacted individuals who, either by publication or by their participation in cooperative group studies or in private practice, had large lymphoma referral practices and tried to get them interested in participating in the trial. We have also contacted the AIDS-related Malignancy Consortium. We have also contacted not only each of the cooperative groups -- that is CALGB, ECOG, and SWOG. So we have made a major, major effort to get in touch with all the major cancer centers and cooperative groups that we are aware of.

DR. KROVASIK: Did you also contact the Lymphoma Foundation, as well?

DR. HOWELL: Yes, and we have in fact asked both the Leukemia Society and the Lymphoma Foundation to make statements in support of this. That did not happen in today's meeting, but I think there is a broad sense of support for making yet another therapeutic option available in this difficult group of patients.

DR. SCHILSKY: Steve, just a safety-related question. How does one grade the severity of arachnoiditis? What is the grading used?

DR. HOWELL: Remember that arachnoiditis is the

capture of a series of symptoms. So it is headache, nausea --

DR. SCHILSKY: Right. That is why I am asking how do you grade it as a single entity.

DR. HOWELL: Right. So when you take -- let's suppose you have a grade 1 nausea, a grade 3 headache, and a grade 2 vomiting. That is a grade 3 arachnoiditis.

DR. SCHILSKY: So you grade it by the severity of the worst symptom in the complex.

DR. HOWELL: That is correct. That is correct. So that further reiterates the fact that most of the arachnoiditis that is occurring here is really quite mild and easily managed.

DR. DUTCHER: Dr. Simon?

DR. SIMON: A couple of questions. Maybe I missed this. Was crossover permitted of the patients who were initially on ara-C?

DR. HOWELL: Crossover was permitted only at the very, very end -- no, I am sorry. It was not permitted. I apologize. That was on the solid tumor trial.

DR. SIMON: Okay. Secondly, could you say a little more in terms of details how you computed those curves of time to neurologic progression? How did you handle the patients who went off study, either because of death from systemic disease or because their physician was

recommending -- it sounded like there were patients who were going off study for reasons other than neurologic progression.

DR. HOWELL: Those curves are time to neurologic progression or death, because to be conservative, under circumstances where we could not be sure whether death was accompanied by neurologic progression, death was scored as neurologic progression. All other patients were censored. We have also prepared a similar plot censoring everybody who died of something -- as best we could determine -- was not due to the meningeal component of the disease. It shows the same thing with a small trend.

Note that we are not making a claim on neurologic progression. We believe that this is an interesting thing to observe, but we are in full agreement with, I hope, the FDA staff on this that this is not something that can be validated by statistical comparison. Recall, however, that no statistical comparisons were to be required when we started this whole study project. The patient numbers and the size of the trial are just too small.

DR. SIMON: My third question is can you clarify on the response rate, when did the responses occur?

DR. HOWELL: Nine out of ten of the patients on the DepoCyt arm had responded by the end of the second cycle. None of them have responded by the end of the first

cycle. One of the two ara-C responses had occurred by the end of the second cycle and one occurred later.

DR. MARGOLIN: If I recall correctly, the last time we listened to this drug presented there was a question of confirmed complete responses and complete responses, the difference having to do with the second negative CSF cytology, and in light of that, it does not look like that has come into any of this. Could you please clarify for us what the changes were that you stated that the FDA had made in their assessment of response or benefit in this study versus the previous study or versus your discussions in 1992?

DR. HOWELL: Yes, Kim, the only difference has to do with patients who converted by the end of induction but did not have two sequential negative cytologies. Dr. Williams is correct that the analysis plan was not prospectively called out in the protocol. I want to be clear about that. It was developed in discussion with the FDA at the time the solid tumor trial NDA was submitted, and what it called out was that we would accept patients who met all these four criteria. That is, we would accept as responders and code separately from the people who met all the protocol criteria -- we would code these patients separately, but we would accept them in the response rate. I point out that if you eliminate these patients, all it

does is to ratchet down the total response rate. It does not change the relative response rates, and that was true in the solid tumor DepoCyt versus methatrexate trial, as it is here. So I think this is an issue for debate and discussion, but it is not critical and central to the issue of whether there is some evidence for a difference in response rate.

DR. DUTCHER: Dr. Ozols?

DR. OZOLS: Yes, I am still puzzled how to deal with the cytologies and what they really mean. So if you get down to slide 79 where you say you want us to consider some of the other advantages that this really may have, do you have any data to support that, like decreasing the risk of infection, decreasing the number of visits to the doctor, reducing patient suffering? I mean, those are the kinds of things that may be important, because it is hard to get a handle on any real objective things.

DR. HOWELL: Bob, we tried to collect that data, but as you can imagine in this very sick population who are also coming to the physician for systemic chemotherapy, for radiation therapy, for a whole variety of other reasons, we could not cleanly pull out visits to the physician that were needed for injection of DepoCyt or free ara-C from all the other visits that these patients had or hospitalizations. So the answer is I cannot for good medical reasons cleanly

and cogently pull those data out in a way that I think would be believable. So we do not have information on exactly how many of the patients are -- now, I do have information on the total number of injections received by these patients.

DR. OZOLS: But there is not any more infection, I mean, with the number of --

DR. HOWELL: You know, it is hard to pull that out. A patient gets a systemic sepsis and then subsequently has a contaminated Ommaya.

DR. TEMPLE: Whether to count people without a confirmatory analysis is not so crucial, because as you say, it adds a couple to each group. What is important, as will become apparent, is whether to count people who did not have a central pathology report. You said a number of times that it is totally unreasonable to expect complete central pathology report, and my question is about that. This may be a special oncology problem or something, but ordinarily you think someone makes a slide, he can show it to somebody else, because he has kept it, it is part of the record, and it is there. You know, like trading an x-ray or doing central reading of whether a person had an MRI. That is done all the time in trials nowadays.

Why is it so obvious that that was very difficult, because a lot does turn on this. I mean, the difference between scenario 1 and 2 is -- in some sense, if response

rate is the endpoint, that is the whole game right there. So why is that?

DR. HOWELL: Well, the reality is that it is extraordinarily difficult to get slides out of pathology departments, and I think every active clinician here would back that up. In fact, I head the basic science committee of the Southwest Oncology GYN group, and we are struggling with this issue of how to get the blocks and slides out of pathology departments so that we can do molecular analyses on ovarian cancer before and after treatment. The reality is I do not think there are any major oncology studies in which one succeeded in getting 100 percent review, and in recent years the impediments put up by IRBs are extraordinary. So it is not unexpected that you would not be able to get every cytologic slide and get it to a central pathologist for review.

DR. TEMPLE: These are slides that exist but they will not let them out?

DR. HOWELL: Absolutely.

DR. TEMPLE: Don't they belong to the patient?

DR. HOWELL: No.

DR. TEMPLE: They don't. So, just to paraphrase something, if the mountain won't come to Mohammed, Mohammed could go to the mountain. The central reader could go to that site.

DR. HOWELL: If the IRB says okay.

DR. TEMPLE: So it is IRBs -- is that actually the thing?

DR. HOWELL: The IRBs are a big problem right now, but it is a general problem in the field that not all slides can always be found. They are lost in the cytology department at times. Fellows walk off with the slides, and by the time we come and ask to review them, they are gone or cannot be found.

DR. TEMPLE: Not that you want to hear this problem, is this potentially reparable? I mean, are they still out there waiting to be read?

DR. HOWELL: No, to my knowledge they are not, and Mr. Thomas can comment on it.

MR. THOMAS: We have asked several times --

DR. DUTCHER: Excuse me, could you identify yourself and where you are from, the consultant, please?

MR. THOMAS: David Thomas, from the DepoTech Corporation. We have been asked this question several times. We presented a complete set of central cytologies to the agency as part of the review and, in the case of the missing slides, identified the reasons for that. None of these, as far as we know, were available. One set of slides was destroyed after the patient's death inadvertently. The others have been lost within the hospital. We have gone to

the cytology department. There are no frank refusals to let them go. The major point on this, however, when we looked at the analysis and reviewed the number of missing slides, most of these have to do with patients who had already been excluded for some other reason. So what you got down to was five slides which, had they been present, might have had an effect on the patient's status, and that was the reason for our analysis.

DR. TEMPLE: Well, it may be only five, but it is about two-thirds of the responses.

DR. HOWELL: Only four responses. It could affect four patients.

DR. TEMPLE: Five out of nine responses or only four?

DR. HOWELL: No, there are five slides missing in four patients.

MR. THOMAS: So the expectation from the discordance rate would be on the order of one slide. All of these, of course, were reviewed as negative by the site. One slide might have been positive.

DR. SCHILSKY: Just to clarify so I am sure I am understanding this, while the central pathology review might have had an impact on what the ultimate definition of response was, it would not have had an impact on the conduct of the study, because as I understand it, the clinical decisions were made based on the local cytologist's review.

This was never intended to be real-time central pathology review.

DR. HOWELL: That is correct.

DR. SCHILSKY: So even if a follow-up cytology turned out to be wrong, presumably if the patient was continued on treatment, it was at least the judgment of the treating physician that the patient was doing okay.

DR. HOWELL: That is correct.

DR. DUTCHER: Other questions for the sponsor?

[No response.]

Okay, thank you.

DR. HOWELL: I would just like to say thanks again to the FDA staff. I know that you all worked very hard on this.

DR. TEMPLE: Sorry, one other question. The other important thing, though, does not figure into the response rate, but I want to give you an opportunity to comment on it, is that a lot of potential responses in the ara-C group were not considered responses because a second cyt was not followed up. My count was about five of those, but that could be off by some. There were not very many similar ones in the DepoCyt group. So that, as you will hear, that is considered important. Do you have any comment on that?

DR. HOWELL: Yes, first of all, perceptive. I will show you the situation that evolved here, and this, by

the way, happened in both the solid tumor trial and the lymphoma trial, and the situation clinically evolves from this. Patient comes into the clinic, has a lumbar puncture as a positive cytology. They then go to the OR and get an Ommaya reservoir put in. Their subsequent ventricular cytologies are negative, but they do not see any reason why they should be subjected to more lumbar punctures because they have the Ommaya reservoir, and the doc told them that the reason for putting the Ommaya reservoir in was because they then would not have to have any more lumbar punctures. So that is an operational problem.

Now, you will recall that in the solid tumor study, all of these cases occurred on the DepoCyt arm, right? In this study, by bad luck, all of them are occurring on the ara-C arm. You know, that is just the luck of the draw in a very sick and difficult group of patients, but if we are talking about analyzing studies in the same way, we have to either decide to accept these or reject these and then score responses in the same way, and I would remind you that if we opt to reject these, which we think should be rejected -- that is, we do not think these patients should be considered valuable -- that it does change -- in other words, if you decide to accept these patients, it would change the response rates substantially in the solid tumor trial in our favor.

DR. TEMPLE: Just to make the point, response rate is much more critical in this trial where it is the endpoint than in the other one. So that is probably a reason there is much more fuss about some of these details.

DR. HOWELL: I am sorry, response rate was exactly the same in both studies. The definition of response was identical. The endpoint was response rate in both studies.

DR. TEMPLE: I know, but here it is proposed to be essentially the sole criterion for approval.

DR. HOWELL: I am sorry. You are absolutely correct. I misunderstood your point.

DR. WILLIAMS: Just to follow up on that point. We are not proposing analyzing it any differently. The problem is the ramifications this has for the quality of the data, the potential number of responses that could have been on the ara-C arm that are not being detected. It is just a problem of data quality.

DR. HOWELL: Yes, and the problem with data quality is a problem with the clinical reality of the disease. So we do not dispute at all that the issue of how best to assess responses in this disease is a valid issue to be discussed. Our feeling is simply that if settle on a set of ways of dealing with this for one trial we ought to apply it equally in the other trial. We thought we had done that in a careful way, and so we appreciate a healthy discussion

of the issues on this point.

DR. WILLIAMS: Okay, and you raised that point several times. The default analysis is protocol specified. So we could go to that, if you would like.

DR. HOWELL: I appreciate it. I think I showed you the response rates default analysis would show.

DR. DUTCHER: Any other questions?

[No response.]

Thank you. We are going to take a 15 minute break. We will be back in 15 minutes.

[Brief recess.]

DR. DUTCHER: We are going to proceed with the FDA presentation with Dr. Van de Velde.

Agenda Item: FDA Presentation

DR. VAN DE VELDE: Good afternoon. My name is Helgi van de Velde. I will review the clinical data of NDA 21-041 for DepoCyt on behalf of the Division of Oncology Drug Products of the FDA. The FDA team reviewing this application consisted of all the following people. I especially want to mention Dianne Spillman, project manager; Anthony Koutsoukos, statistics; and the other members of the medical team, Steven Hirschfeld and Grant Williams.

NDA 21-041 was submitted for application for accelerated approval for DepoCyt or liposomal ara-C, which will also be called in this review DTC 101. The indication

is intrathecal treatment of lymphomatous meningitis. The NDA was submitted on October 2, 1998, and the last amendment was received on November 2, 1998. This just reminds me to apologize to the committee that they have not received my review earlier than last week, but we were still receiving data 2 weeks ago.

During my presentation, I will briefly touch on the regulatory history of this product, briefly touch on regulations on accelerated approval, give a brief review of the current literature, followed by a more extensive review of selected aspects of the current submission, followed by a summary.

In October 1992, a meeting between the sponsor and the FDA proposed a controlled study design for neoplastic meningitis consisting of three separate arms: solid tumors, lymphoma, and leukemia. In each arm, the patients were to be randomized to either DepoCyt or an active control. In the lymphoma group, the control group was going to be intrathecal ara-C, and it was stipulated that primary CNS lymphoma was allowed on the lymphoma arm.

The ODAC committee in December 1997 reviewed NDA 20-798 for treatment of carcinomatous meningitis in solid tumors. The committee voted that the submitted studies were not adequate and well controlled -- 7 to 3 -- and that the data did not represent substantial evidence of efficacy --

10 to 0.

In August 1998, and based on reported -- not reviewed -- reported promising results, FDA invited the company to submit application for accelerated approval for the lymphoma indication.

Some aspects on the regulation of accelerated approval. For accelerated approval, in order to qualify for accelerated approval, a drug must show meaningful therapeutic benefit to patients over existing treatment. The approval can be granted on the basis of adequate and well-controlled clinical trials establishing that the drug has an effect on a surrogate endpoint -- in this case complete response -- that is reasonably likely to predict clinical benefit.

The approval comes with the requirement that the applicant study the drug further to verify and describe its clinical benefit.

Short review of the literature -- and I presume I can skip over most of these data -- I just want to point out that the natural history of lymphomatous meningitis is not well-documented, but there are reports in the literature about untreated leptomeningeal carcinomatosis, which is normally fatal 4 to 6 weeks after diagnosis.

Current treatment options available for lymphomatous meningitis are radiation, systemic chemo, and

intrathecal chemo, intrathecal chemo with methotrexate, ara-C, and steroids.

An optimal standard of care treatment has never been prospectively defined and, indeed, no treatment has been approved by the FDA. The most common approach is a combination, as you heard, of radiation therapy and intrathecal chemotherapy, and it was already pointed out by the sponsor that ara-C only as a first-line intrathecal has only been reported in a small number of patients.

What are the outcomes of this standard of care approach as published in the literature? Neurologic symptoms are reported to have improved and stabilized in 80 percent of the patients. However, neurologic deficits are often fixed. Cytologic CSF clearance are reported in the literature in 73 to 100 percent of patients on first-line intrathecal chemo, and I cited a couple of the recent papers.

I would like to point out that none of these figures -- that all of these figures come from trials that probably never have gone through as rigorous review as the data we are reviewing today.

Based on the literature review -- I think we can skip that slide -- there is agreement that overall survival may not be influenced by effective intrathecal treatment. I would like to stress that there is no agreement in the

literature how to assess response to treatment of lymphomatous meningitis. All of the studies take CSF cytology clearance into account, and they all request a confirmed specimen at least 1 week apart. Most use neurologic status as an additional criteria, and some use radiologic disappearance of meningeal masses or normalization of CSF chemistry as additional criteria.

Age, performance status, systemic disease, and cranial nerve deficits have been shown to be prognostic factors in neoplastic meningitis. There are reports in the literature that systemic chemotherapy only is able to clear CSF cytology, and it seems from some published trials that lymphomatous meningitis in the complex of primary CNS lymphoma has a better prognosis than lymphomatous meningitis in the complex of non-CNS lymphoma. Therefore, the distributions of these factors need to be assessed in randomized trials for lymphomatous meningitis.

Study objectives you already heard from the sponsor. Primary efficacy endpoints were response rate, time to complete response, duration of complete response, and time to relapse. Secondary efficacy endpoints, neurologic symptoms and quality of life.

The second objective was to determine safety. The third objective was to compare the need for dexamethasone for symptomatic control of drug-related toxicities.

I can skip these couple of slides. It was described by the sponsor. Study regimen, treatment during the induction phase and treatment during the consolidation and the maintenance phase.

Let's focus on the characteristics of the patients on the trial. Seventeen patients were randomized to DTC 101, 16 to ara-C. There is a pure balance in the distribution in the two arms for AIDS-related lymphoma, for Karnofsky performance status, and for CNS radiation prior to study entry.

This was the status of systemic disease of the patients before they went on trial. I just would like to point out that the number of complete responders prior to study entry was equally divided over the two groups, that there were a lot of patients in which the systemic disease status was actually unknown or inaccessible, that there were more progressive disease patients on the ara-C arm than on the DTC arm, and that there were more stable disease patients on the DTC arm than on the ara-C arm.

These are other treatment characteristics that are not as well-balanced in the two groups. Median age actually is in favor of the ara-C group. The other are actually in favor of the DTC group. Nine versus four received concurrent systemic chemo; three versus one received concurrent CNS radiation. Six versus two had primary CNS

lymphoma, and five versus eight had cranial nerve palsies.

I would like to point out that one patient on the DTC arm had a positive CSF flow study, had CSF compartmentalization as shown by a positive CSF flow study. The protocol is very clear that a patient with a positive CSF flow study not reversed prior to start of the treatment is actually ineligible. So this patient should have been considered ineligible.

Let's focus first on efficacy. As I said, one patient was ineligible due to this positive CSF flow study, and two patients, one on each arm, never received any intrathecal therapy for various reasons.

Complete response, as defined by the original protocol, had two criteria. First, two consecutive negative CSF cytologies, at least 3 days apart, in the absence of neurologic progression.

Now, what does the protocol say about how to assess cytologic response? On day 29, after the induction phase, a CSF sample needed to be taken from an initially positive site. If the sample was positive, the patient was considered a non-responder and should come off study. If the sample was negative, the cytology was negative, confirmatory samples had to be drawn from all initially positive sites. The protocol is very clear about that. When this has to be done -- and I quote the protocol

literally -- it has to be done between weeks 5 and 6, day 32, and apparently this is a confusing statement leading to several potential interpretations.

The protocol is also very clear that a blinded central cytopathology reading is required for all patients and is going to be final. Atypical readings should be considered negative per protocol. Suspicious readings should be considered positive by protocol.

During our analysis of the cytologic response assessment, we found several violations of these guidelines, and we would like to subdivide them into major violations, minor violations, and intermediate violations.

Major violations we consider those patients who received forbidden treatment while on study, and this happened to two DTC patients. One had high dose intravenous ara-C methatrexate, which was forbidden by protocol. The other patient had whole brain radiation therapy, which was forbidden by protocol. This actually was the same patient who was ineligible to start with.

Then there are a couple of issues on CSF sampling. Three patients on the ara-C arm, versus zero on the DTC arm, did not have their initial site checked. So these are patients who start with a positive lumbar puncture and never have a lumbar puncture controlled again.

Two patients on the ara-C arm and one on the DTC

arm did not have all their initial sites checked. So these are patients who started off with a positive intraventricular and a positive lumbar puncture, and only the intraventricular site is checked.

Then there was one patient on the ara-C arm who got a supplementary site checked. This patient had a positive intraventricul cytology, did not have a lumbar puncture. However, at day 29 his intraventricular cytology had cleared, but he got an additional lumbar puncture which still contained malignant cells. So this patient was considered a non-responder, because a supplementary site not required by protocol was checked.

Then there were three patients on the DTC and four on the ara-C arm who did not get a confirmatory sample, and this is a pretty important part, as illustrated by the fate of three of these patients and on one patient on the ara-C arm. Actually, so these patients did not receive any confirmatory sample within the prescribed time window, but the next available cytology at the 50 or 45 or later, the next available cytology was actually positive. So it is very hard to call these patients responders.

Let me just point out that these numbers are not mutually exclusive. Some patients can have, for example, a forbidden treatment and no confirmatory sample or an initial site not checked and no confirmatory sample.

Minor violations, we would call these violations in which the initial sample was either drawn late or the confirmatory sample was drawn late, and we consider these a minor violation and we will accept it at response analysis, first of all, because the initial protocol -- the protocol initially was confusing, and secondly, because a negative cytology at day 45 for a day 50 for the patient probably means as much if not more than a negative cytology at day 32.

Intermediate grade violation is the whole issue about central pathology, and this is an issue in seven DTC patients and one ara-C patient. There is no doubt in our minds that the central pathologist had a tendency to read more slides as positive than the local pathologist, and this is illustrated by the following analysis.

This analysis looks at the number of slides that were read negative or atypical by the local reviewer and read positive by the central reviewer. Of the 11 samples read as atypical by the local cytologist, 6 or 55 percent was called positive by the central reviewer. For the 140 samples called negative by the local reviewer, 32 or 23 percent is called positive by the central reviewer. So from that we conclude that a sample read as atypical by the local reviewer has a likelihood of about one in two of called positive by the central reviewer, and a negative sample read

by the local reviewer has a likelihood of about one in four of being called positive by the central reviewer.

So that leads us to the three different scenarios you already heard about. The first scenario, we are going to reevaluate the patients that either got their response analysis strictly according to protocol or these patients in which just the fact that the CSF samples were drawn late as the only violation of the protocol were still acceptable. In that scenario, we have seven evaluable patients on the DTC arm and eight on the ara-C arm. One of the eight ara-C patients responded. Three of the seven DTC patients responded. Under here is the list of why these patients were considered non-evaluable, and a lot of them by that criteria non-responder. That is the forbidden treatment, the CSF sampling errors, no central pathology, or untreated ineligible patients. I would like to submit to you that there is an imbalance here in the ara-C group versus the DTC group in the number of patients that would potentially have qualified as responders but just were not able to be called responders because of these CSF sampling errors.

Scenario 2 allows not only late CSF samples, but also allows lack of central pathology. If we accept local pathologists' results, we end up with the same number of patients for the ara-C group, one out of eight, but there are four more patients evaluable on the DTC group, and these

four patients are also then called responders. Again, what is excluded from this analysis are the patients with forbidden treatment, CSF sampling errors, or untreated ineligible patients.

The third scenario, which is clearly unacceptable for the FDA, is to forgive all protocol violations and only excludes from the analysis those patients who never got any treatment at all. That would lead to 16 evaluable patients, 12 of which responded on the DTC arm, 15 evaluable patients on the ara-C arm, 7 of which responded.

So if we put that together in one table, I would like to submit to you that in whatever scenario we look, the number of responders on the DTC arm is actually higher than on the ara-C arm.

What about patient characteristics and response? We did not find any obvious association with response for age, performance status, on-study radiation therapy, cranial nerve palsies, or systemic disease status.

I would like to draw your attention to the distribution of systemic chemotherapy and CNS lymphoma for the evaluable and responding patients into two scenarios. Let's look first at scenario 1. In the ara-C group, we have eight evaluable patients. None of the eight got systemic chemotherapy, and none of the responders got systemic chemotherapy. Of the seven evaluable patients on the DTC

arm, three got systemic chemotherapy, two of which responded.

In scenario 2, these numbers remain the same for the ara-C group. For the DTC group, of the 11 evaluable patients, four received systemic chemotherapy. Three of these four were actually responders.

What about CNS lymphoma? Of the eight evaluable patients in scenario 1 for ara-C, one had primary CNS lymphoma, and this patient did not respond. Of the seven evaluable patients of the DTC group, two had a CNS lymphoma, and all two patients responded.

In scenario 2, the number for ara-C remains the same. For the DTC, four patients had primary CNS lymphoma, and all four patients responded.

I think I can skip this slide. This was already explained by the sponsor.

Time to neurologic progression, briefly, was 78 days versus 51 days, with a median overall survival of 82 days and 64 days. In our analysis, the number of 6-month survivors and 12-month survivors was not clearly different in the two arms.

Prospectively defined quality of life instruments were Karnofsky performance score, mini mental state exam, and FACT-CNS questionnaire. I would like to point out that there were not enough data during the consolidation and the

maintenance phase for any of these quality of life instruments to draw any meaningful conclusion or to do any meaningful analysis. So the only data we have is actually comparing a baseline versus day 29 measurement.

As was already pointed out by the sponsor, the numbers are low. The numbers of available patient data are low, certainly on the ara-C arm, for the mini mental state exam and the FACT-CNS, also for the DTC arm. For the patients who had data at baseline and day 29 for the Karnofsky, there was a tendency for the DTC patients to improve -- they have an improved Karnofsky -- and for the available patients a tendency for a decreased Karnofsky at day 29 for the ara-C group.

So our conclusions from the efficacy analysis are that DTC 101 has activity in lymphomatous meningitis patients. The response rate varies according to the analysis. The response rate for DTC is higher than for ara-C, but imbalances in CSF sampling violations preclude a formal comparison.

Second study objective, safety. First, the extent of exposure. The patients on the DTC arm were longer on treatment and received more cycles of DTC than the ara-C patients. The average number of cycles for DTC was 5.2 cycles per patient and for ara-C 3.45 cycles per patient. Therefore, the likelihood or the risk that a patient on the

DTC arm had a drug-related adverse event is higher, just because he is exposed to drug longer, and we concur with the sponsor's interpretation that we should look at adverse events per patient and per cycle.

In the safety analysis, 27 patients were included. This is a table taken from the sponsor's analysis on drug-related adverse events by cycle. The drug-related adverse events noted are headache, nausea, vomiting, asthenia, fever, pain, meningismus, confusion, somnolence, and neutropenia. I would like to point out that, except for asthenia, for all other drug-related adverse events, the frequency even after adjustment for cycle, the frequency is higher on the DTC arm than on the ara-C arm.

The number of headaches on the DTC arm is quite high. It was reported in 27 percent of all treatment cycles.

This is another graph taken from the sponsor's analysis comparing drug-related adverse events, again per cycle, and comparing to pre-study. We can do so because a lot of these drug-related adverse events as headache, nausea, vomiting, et cetera, can be caused by drug but can as well be caused by the lymphomatous meningitis disease.

It is clear from this analysis that the frequency of these adverse events on both arms decreases while on treatment, I presume not only because of the chemotherapy

but also because of all the concomitant supportive care that the patient received. However, the frequency of serious drug-related adverse events -- these are the black boxes -- and the total number of adverse events is different or is higher on the DTC arm than on the ara-C arm.

This is the sponsor's analysis on headache per treatment cycle for the two patient groups, and again, you appreciate that the frequency of headache on the ara-C is certainly much lower than on the DTC arm.

This is confirmed by our own analysis of the safety database. We found 10 patients on the DTC arm and 5 on the ara-c arm who got new onset headache. Six versus zero had new onset serious headache. Eight versus one had new onset drug-related headache, and four versus one had new onset serious and drug-related headache. This is also apparent from the reported analgesis use used for headache per days per cycle, five on the DTC arm versus 1.5 on the ara-C arm.

In the previous NDA submission, chemical arachnoiditis frequency was addressed by the sponsor, and this is a quote from the sponsor's own analysis, that 13 DTC 101 patients developed chemical arachnoiditis serious enough to warrant hospitalization versus one methotrexate patient developing chemical arachnoiditis.

DR. WILLIAMS: Helgi, I just wanted to interrupt

you on that. I think the sponsor is correct that that came from -- we have tried to use their own words, but it came from their overall summary, so it included another trial of DepoCyt.

DR. VAN DE VELDE: The third study objective was the use of dexamethasone. Let me remind you that there was a required use for dexamethasone, 4 milligrams po or IV bid for 5 days per cycle, required for protocol. By the sponsor's analysis, the compliance for this required use was higher on the DTC arm than on the ara-C arm, and obviously the required use was a prophylaxis for chemical arachnoiditis. Moreover, the protocol allowed additional use of steroids in case arachnoiditis developed.

We looked at the total dose of dexamethasone that the patients received on the two arms. Nine versus six patients received more than 50 milligrams per cycle. Four versus two received more than 100 milligrams per cycle, and the median dose was higher on the DTC arm than on the ara-C arm.

As steroids are known to also have an anti-lymphoma effect, we looked whether the differences in the total dose of dexamethasone during the induction phase might have influenced the complete response rates in the two arms, but that does not seem to be the case. The median and mean induction dose on the two arms were pretty similar. So that

certainly will not affect response rates.

As a summary of risks and benefits, DTC 101 has activity by CSF cytologic response in patients with lymphomatous meningitis. The dosing schedule of DTC 101 is more convenient than that of ara-C. The DTC 101 group had more adverse events per patient per cycle, had more serious adverse events per patient per cycle, had more headache per patient per cycle, and had more dexamethasone use per patient per cycle.

This leads to the following critical questions for the committee. Is cytologic complete response in the absence of neurologic progression an adequate surrogate reasonably likely to predict clinical benefits? Second, is this study an adequate and well controlled study to determine cytologic complete response rates? I would like to point out that in our scenario 1, 15 out of 31 patients were evaluated according to protocol and that a disproportionate number of inadequate CSF sampling occurred on the ara-C arm.

The third question is do cytologic complete response rates of DTC 101 and ara-C establish that DTC 101 provides meaningful advantage over existing treatments?

Thank you.

DR. DUTCHER: Thank you.

Questions from the committee for the FDA?

Dr. Williams?

DR. WILLIAMS: Helgi, you may not be able to answer this, and we will go to the company if you cannot. In terms of their analysis of time to neurologic progression, they included deaths as events. We did not pay a lot of attention to this analysis because it is not significant. The main thrust is the surrogate. But it seems to me that deaths might not be an appropriate event if we are supposed to be measuring neurologic effect, and if there is a large number of deaths, it could just be underlying prognosis or disease. So do you know the number of deaths versus the number of neurologic events versus censoring in that analysis?

DR. VAN DE VELDE: No, I would like to defer that to the sponsor.

DR. WILLIAMS: Okay, time to neurologic progression. You said that is neurologic progression or death, right? The question is the number of actual neurologic events on the analysis versus the number of deaths versus the number of censored patients.

DR. HOWELL: I can show you the curve, if you want.

DR. WILLIAMS: No, the curve does not show the numbers, unless you have the numbers on the curve.

DR. HOWELL: It is two on each arm.

DR. WILLIAMS: Two what?

DR. HOWELL: Two patients have been censored in each arm.

DR. WILLIAMS: How many deaths versus how many neurologic progressions?

DR. HOWELL: Two deaths. All the rest are neurologic progressions. Two in each arm.

DR. WILLIAMS: Then all of the rest of the patients in this -- how many then, the number of neurologic progression events you actually have on the study?

DR. DUTCHER: Well, early on you showed deaths on both arms, in the first two weeks of treatment.

DR. HOWELL: Grant, I do not have a number for you right off the bat, but I can grab it in the next few minutes. These are all patients who died with meningeal involvement. So in terms of time to neurologic progression, all the events except two deaths in each arm on that curve are neurologic progressions as opposed to deaths.

DR. WILLIAMS: How many is that again?

DR. HOWELL: It is two deaths on each arm. All the other events are true neurologic progressions.

DR. TEMPLE: Helgi, one of your slides which is called characteristics of patients number three, you described certain characteristics as favorable, including a number that you described as favorable to DepoCyt. How can

you tell what is favorable and what is not -- presence of systemic disease and things like that -- with respect to the outcome that one is looking at here. You might have an idea about what is favorable to survival, but how do you know it is favorable with respect to clearing of CSF?

DR. VAN DE VELDE: Okay, the four prognostic factors that I mentioned -- age, Karnofsky performance status, systemic disease, and cranial nerve palsies -- have been looked at as prognostic factors for patient benefit being time to neurologic progression and overall survival, not only looking at complete response rate, and this comes from a randomized trial of neoplastic meningitis in which lymphoma was a subgroup.

Does that answer your question?

DR. TEMPLE: No, not quite. I assume that when one talks about the groups being unbalanced, one means with respect to one or more of the various endpoints that are being looked at. Well, one of the main endpoints here is CSF clearing, and it was not easy for me to tell -- it was actually not those four; it was the next four, like presence of systemic disease and things like that. It was not obvious how those would relate to the likelihood that you would clear your CSF, which is the relevant endpoint that one is worried about imbalance with respect to. Now you might also be worried about time to neurologic progression

or death, and they might have different implications for that.

Do you know the slide I mean? It is called characteristics of patients 3.

DR. WILLIAMS: I think prospectively you might have expected an association between response and some of these factors, and he is talking about by looking into the data there was no strong evidence that in these data there was a strong association. Of course, none of these could be statistical to start with. It is just like four versus zero.

DR. TEMPLE: Maybe this is not important, but the slide showed CNS radiation during study prior to response evaluation, primary CNS lymphoma, cranial nerve palsies, and those were characterized as somewhat favoring the DTC 101 group. My question was how can one know that, whether they favor or disfavor or -- it was not obvious to me what the implication of those things were. So I thought you could explain it.

DR. VAN DE VELDE: Okay, cranial nerve palsies have been reported in the literature as a negative prognostic factor. So that is the reason I found that DTC, the fact that there were more on the ara-C group than on the DTC group as in favor of DTC.

DR. TEMPLE: Now that is for survival, right?

DR. VAN DE VELDE: That is for patient benefit. That is for clinical endpoints. This is not especially for complete response, as such.

DR. TEMPLE: Okay, but, you know, depending on the endpoint you are looking at, that is what matters here. You are asking what might predict a favorable CSF clearing response, and it was not obvious to me -- but then I do not know much about this -- how one would know whether those were favorable or unfavorable characteristics for that endpoint.

DR. VAN DE VELDE: No, I do not think that specifically for this endpoint these patient characteristics have been evaluated.

DR. TEMPLE: Okay, like for survival or time to death and stuff like that.

DR. VAN DE VELDE: Yes. I would like to point out that there are certainly reports in the literature that systemic chemotherapy given only without intrathecal treatment is able to clear CSF cytologies.

DR. TEMPLE: Okay.

DR. SCHILSKY: Well, just to be fair, I will ask you the same question I asked the sponsor, which is it seems to me that your analysis of the study focuses a great deal of attention on cytologic response, and while I think that is probably important, I would suggest that most clinicians

and certainly all patients would consider lack of neurologic progression or neurologic improvement more important than cytologic response. So based upon your extensive review of the case report forms, what is your impression with respect to the neurologic response or neurologic progression or lack of neurologic progression in the two treatment groups?

DR. VAN DE VELDE: Well, first of all, the reason we are focusing on response rate is that this is the surrogate endpoint that the --

DR. SCHILSKY: But the response rate in the study has two components to it. One is clearing the CSF and one is lack of neurologic progression. So what I am interested in hearing about more than clearing of the CSF is the lack of neurologic progression.

DR. WILLIAMS: Helgi, perhaps there is a misunderstanding. We included lack of neurologic progression in our response analysis, as did the sponsor. Every responder, it was assumed to be not progressing at the time, he was called a response. So we have included it.

The time to event endpoint we do not think is really valuable in such a small number of patients.

DR. SCHILSKY: What I am trying to understand, Grant, is is it anybody's impression that these patients either got better or at least did not get worse as a result of being treated with DepoCyt?

DR. WILLIAMS: I think it is our impression that we do not have a large enough study to answer that question. It was a part of the response endpoint, and we are evaluating this as a surrogate for accelerated approval. If we had enough to evaluate time to neurologic progression in the manner it should be evaluated, we would be asking for full approval.

DR. DUTCHER: Well, on that topic, we just heard this was one of the most difficult studies to complete. What do you see as a confirmatory that would allow us to go further than accelerated approval? The pediatric study, or what is being proposed?

DR. WILLIAMS: Those discussions really have not taken place. It would be a necessary thing to decide if you did vote for approval, and it certainly could be your last question to discuss if you do. But we do not require approval in the same setting. So I have heard discussion of pediatrics. You could think about adjuvant settings, et cetera, just basically in the same disease, and Dr. Temple may want to make some comment.

DR. TEMPLE: Well, it has not been discussed yet. You may at some point want to ask the sponsor what further studies they think they could do. I mean, one of the things that immediately occurs to my mind, hearing the previous discussion, is that if there are a lot of people who are

failing other ongoing studies because of meningeal complications, that is a perfect group to put into a study. So it may be some of the ongoing studies could be used if people could persuade the people conducting them to add arms to that. But we have not gotten into that. It is something the sponsor has to deal with.

On some of the other things that came up, if there had been clear beneficial effects on neurologic progression, we would all be throwing things and feeling good. Accelerated approval exists for those situations where those data are not available but where in our judgment and with the help of our advisors we think a reasonable surrogate exists that would make the drug available sooner while the real benefit data are coming in.

DR. SCHILSKY: Just to follow up on that, could I ask for clarification with respect to accelerated approval about the need to demonstrate, as it is stated here, meaningful therapeutic benefit to patients over existing treatments. To me, that implies a randomized clinical trial with sufficient statistical power to demonstrate a benefit compared to some standard, some existing treatment. It seems fairly clear that from the time that these studies were first designed that there was never a goal of demonstrating statistical superiority to some existing treatment. There was only a goal of having two

contemporaneous groups of patients to try to make relative comparisons. So I guess I am confused about the importance of being able to satisfy the accelerated approval criterion with an appropriately powered comparative trial.

DR. TEMPLE: Well, remember, the data you have is only about a surrogate. So the accelerated approval concept has to be based on the finding of the surrogate and the belief that that is meaningful. If you concluded, however, that the surrogate endpoint was reasonable evidence of effectiveness, you could certainly take into account the ease of administration and things like that. That is highly pertinent, but you would first have to conclude that there was reasonable evidence of effectiveness based on the surrogate.

DR. SCHILSKY: Right, but, for example, in the presentation we heard, on one of the conclusion slides about efficacy, it is concluded that DepoCyt response rates are higher than ara-C, but, in capital letters, but imbalances in CSF sampling violations preclude formal comparison. Well, there was never intended to be a formal comparison, as I understand it. So I am not sure why the but in capital letters there.

DR. WILLIAMS: Well, actually I do think that there was the possibility of a formal comparison with a very large effect, which the sponsor was indeed claiming. It was

statistically significant according to their analysis.

But I do agree with the sponsor's suggestion that it is possible -- and Dr. Temple -- that an advantage could be defined as convenience, et cetera. But then you would also have to consider toxicity.

DR. OZOLS: Getting to the toxicity, it has been raised several times that it is sort of not responding neurologically, it is just not progressing, and one of the ways these patients present is with headaches and nausea from the increased intracranial pressure, but now we are seeing quite a bit of increased toxicity with those two parameters. So how do you assess that global assessment? Are they getting better or worse when you have so much more headache in the treated patients?

DR. VAN DE VELDE: Well, you assess them by how they are graded.

DR. OZOLS: But were they graded neurologic -- the headaches were worse, or they were worse due to the toxicity?

DR. VAN DE VELDE: Well, it is hard for me to say where it comes from. What I know is that on the ara-C arm, certainly the frequency of headache went down. Clearly on the DTC arm the frequency of headache did not go down, and actually the grade of headache, you know, a lot of serious headaches, grade 3 and 4, which was not present as

pretreatment. That is the only way you can compare is to the pretreatment situation.

DR. WILLIAMS: I think the global exam, I doubt, included headache.

PARTICIPANT: [Comment off-mike.]

DR. VAN DE VELDE: I am talking serious, called grade 3 and 4. This is taken from your own graph.

DR. HOWELL: They are all grade 3. There is no such thing as a grade 4 headache.

DR. WILLIAMS: The point I was making is that the global exam, the global analysis of neurological exam, I doubt it was based on headache. It was on neurologic exam, and I am not sure that headache was included. I agree it is a symptom, but I am not sure -- maybe the sponsor can clarify whether or not headache was taken into account in the global.

DR. HOWELL: First of all, global assessment is exactly that. It takes into account all of the patients neurologic findings, symptoms, signs, the history of what has been happening to that patient neurologically, any laboratory data that is available that might indicate a trend in one direction or another. This is what happened in the headache situation, and I would caution you that this kind of an analysis simply tells you the number of patients in each cycle who have headache. I do not think with these

numbers it is appropriate to determine what the rate of decrease in the frequency is when you are dealing with such tiny, tiny numbers. I do not think the data would support that.

We are in agreement that the headache is a little bit more on the DepoCyt arm, but this is largely low-grade headache and it is the tradeoff that you make for getting a much, much higher response rate and a more effective form of therapy. So it is a straightforward tradeoff.

This is the slide that shows grade 3 headache, and I would point out that there just is not a lot of grade 3 headache going on in these patients. The white area is time without grade 3 headache. So the white area is time that we spend with headache if it occurs at all that can be managed with aspirin or acetaminophen.

The other point is that this headache is very transitory. You know, the median duration of a headache that occurs is a discrete episode. That is, where it is clearly separate from the underlying disease related headache is less than 1 day.

DR. MARGOLIN: This would probably be more of a question to the sponsor. Assuming that any postmarketing trials that are done are going to be done in large populations of patients with a much better overall prognosis, such as children with leukemia, is there anything

known, say from animal models, about long-term neurotoxicity of DepoCyt?

DR. HOWELL: The only information we have is from humans who have received more than 10 cycles. Sorry, Dale can answer the animal question. I can answer the human question, which is that there is no suggestion of cumulative toxicity up to 10 cycles or more, and I would point out that when we start worrying about neurologic toxicity, there is usually a lot more to worry about in methatrexate than in ara-C when you are talking about long-term toxicity, particularly in kids, particularly in kids getting radiation therapy.

DR. JOHNSON: Dale Johnson from Chiron(?). We did a four-cycle study in non-human primates looking at DepoCyt versus two different control groups. One was the actual liposomal control and the other one was a saline control, and there really is no long-term neurological effects.

DR. DUTCHER: Other questions?

[No response.]

Okay, thank you very much.

One more?

DR. TEMPLE: I just wondered if you could add anything about the recurrent question of central reading. I think you recorded the phrase -- I wrote it down and put it in quotes -- that it was required for all patients. Dr.

Howell has said, well, they wanted to get it for all patients, but there was an analysis plan that said if you cannot, then use the local reading. Do you have any further comments on that question?

DR. VAN DE VELDE: Well, the only thing I can do is quote you the original protocol, and the original protocol says, after talking about the local cytopathologist: in addition, an independent cytopathologist will be appointed to review all cytology results after the patient has completed the study. This evaluation, not the local cytopathology review, will be final for purposes of the efficacy review. Procedures will be added to assure that this centralized review is performed blinded to the patient's treatment and to the results of the previous local evaluation. All investigational sites must comply with the central cytopathology requirement. There is no mention in the original protocol that in absence of central pathology data, we were just going to accept the local cytopathology data.

DR. TEMPLE: Is there anything beyond the original protocol? I mean, it is perfectly obvious they were trying to do a rigorous blinded independent analysis. At least that was the intent. Is there anything else that comes later that says, oh well, sorry, never mind, and is therefore still part of the protocol or anything to add to

that? That is really all I am asking.

DR. WILLIAMS: We have numerous times been told about an analysis plan. First it was said that it was in the protocol. Then they said it was in the analysis plan and that we have agreed to it. I do not believe we have any sort of formal agreement about any analysis plan. We may have overlooked something the first time around, but that does not mean we agree with it.

DR. HOWELL: To be clear on this point, Dr. Williams is correct that the protocol is silent at the time it was written, back in 1992, about the specifics of how to deal with missing data. The plans and the rules for dealing with missing data were worked out in meetings with the FDA at the time the solid tumor NDA was submitted.

Now, I do not want to get into a semantics argument. You know, the NDA was accepted. It was reviewed. I do not know whether that constitutes agreement or not agreement. I do not think that is important. What is important is that we made a clear attempt to establish a set of rules for how to deal with missing data, and we used exactly the same set of rules in dealing with the lymphoma trial that we have dealt with in the solid tumor trial. So exactly when and who agreed to what I think are less important than the issue that, yes, a clear anticipation that we would not get a 100 percent oncology slide review --

we never have in any trial that I have been associated with -- and a clear way of trying to deal with that in a reasonable medically rational way which has strong precedent in all the cooperative group trials. This is how we do it.

DR. SCHILSKY: I guess just one more question to the FDA. Since there is so much controversy about how to interpret efficacy and response, let me just ask you this. In your review of the study, applying whatever efficacy criteria you choose to apply, however you think in your mind is best to evaluate the data, is there any scenario that you have uncovered in which DepoCyt does not appear to be at least as efficacious as free ara-C?

DR. VAN DE VELDE: I think I have -- well, I have given you the answer. I focused in my review on the response, and in whatever scenario you look at, it looks better for the DTC than for the ara-C. I cannot recall other analyses that were actually in favor of the ara-C group. However, I would like to caution that a lot of these ara-C patients actually -- the number of ara-C patients certainly during later phases of the trial become quite small. But, no, the answer is, just without analyzing them myself, just looking at the sponsor's analysis, there were no endpoints that were really in favor of ara-C.

DR. DUTCHER: Last chance.

[No response.]

Thank you.

Any other comments, discussion, before we address the questions?

[No response.]

Agenda Item: Discussion of Questions to the Committee

Do you have the paper in the folder, the blue folder? The applicant seeks accelerated approval for DepoCyt in the treatment of lymphomatous meningitis based on results of trial 92-001. Thirty-three patients were randomized to intrathecal treatment with DepoCyt or ara-C. The primary objective was to compare the rate of response, defined as complete cytologic response and the absence of clinical progression, on the two arms.

The following is the summary of the accelerated approval regulations. The accelerated approval regulations were finalized on December 11, 1992, and are found in 21 CFR section 314.500. There are several critical statements in the regulations.

This regulation applies to drugs that have been found to provide meaningful therapeutic to patients over existing treatments, e.g., ability to treat patients unresponsive to or intolerant of available therapy, or improved patient response over available therapy. FDA may grant marketing approval for a new drug product on the basis

of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Approval under this section will be subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit. The applicant shall carry out any such studies with due diligence.

So the first question is based on initial reports of promising results, the FDA invited the applicant to submit an NDA for DepoCyt for the treatment of lymphomatous meningitis to be evaluated according to the accelerated approval regulations, utilizing complete cytologic response as a surrogate endpoint for patient benefit. Does the committee agree that complete cytologic response with the absence of neurologic progression is a surrogate endpoint that is reasonably likely to predict benefit in patients with lymphomatous meningitis treated with intrathecal therapy?

Who would like to comment?

Dr. Schilsky?

DR. SCHILSKY: I agree.

DR. DUTCHER: I agree.

All those who would vote yes on this question?

[Show of hands.]

Seven, and Ms. Beaman voted no. So seven yes and one no.

DR. TEMPLE: Can I just ask a question so that you will make it clear? In considering carcinomatous meningitis, the conclusion in that case on a similar question was no. I assume --

DR. WILLIAMS: We did not ask that question, I do not believe. We asked if it was, the actual whole ballpark, not just a surrogate.

DR. TEMPLE: Fair enough. I will not dispute that. Is that because you believe the kind of tumor and the nature of the seeding is such that CSF seeding is more meaningful? I mean, is that the kind of reasoning? Because we are going to need to explain to people in the world about why this is a reasonable endpoint. Would that be a summary of your reasoning?

DR. DUTCHER: I think the reasoning is that you have several groups of people in this study. You have people with primary CNS disease who may be more amenable. Lymphoma is a more chemo-sensitive disease, and we have all seen responses with intrathecal therapy. So I think we think we are working with something we can work with here so that it may in fact lead to meaningful results, probably in conjunction with systemic therapy as well.

DR. TEMPLE: Okay, that is helpful. Thank you.

DR. MARGOLIN: Just a clarification, Dr. Temple is right; that exact same question was asked the last time, and the vote was five to five, cytological response and the absence of neurologic progression for solid tumors.

DR. WILLIAMS: But it was not done in the context of accelerated approval. There is a much different burden of proof, substantial evidence versus reasonably likely.

DR. TEMPLE: But Grant, if the vote had been a strong hurrah, it could have led to accelerated approval. So it is a related question. I am content with the answer.

DR. DUTCHER: Question number 2. Evaluation of response rate is very difficult in this trial, due to multiple protocol violations, e.g., administration of forbidden therapies, inadequate collection of CSF samples, and lack of crucial central pathology review. Given these data, FDA would propose three different scenarios for interpreting response. One, only patients for whom response data were collected according to the protocol or who had minor protocol violations, such as late confirmatory CSF samples, are considered to have cytologic response. Two, patients who, in addition, had no central pathology review of data are also considered to have cytologic response. Three, all protocol violations are ignored.

Then there is a table which shows that these three

different scenarios would lead to the following interpretations of response rates, which I will let you review.

The third scenario, which was to ignore protocol violations, is unacceptable for FDA. Given the discordance between central and local pathology review, FDA considers scenario 1 the most acceptable interpretation. Median duration of response on the DTC 101 arm was 38 days for scenario 1 and 59 days for scenario 2.

Is study DTC 92-001 an adequate and well-controlled study for the purpose of determining the cytologic complete response rate with absence of neurologic progression of treatment with DepoCyt versus ara-C?

One thing I do not think we discussed, and I do not necessarily mean we should go back and do so, but just to point out that we did not talk about the possibility of differences in times of sampling in comparing, if you choose to compare, durations of cytologic response between DepoCyt and free ara-C.

DR. SIMON: You know, previously we were talking about the requirement for accelerated approval, one component of it being adequate and well-controlled trials establishing that the drug product has an effect on a surrogate endpoint. This question words it differently. It says adequate and well-controlled study for the purpose of

determining the cytologic response rate. I think this is a stronger requirement.

DR. WILLIAMS: Well, the next question asks is the effect big enough. This is just -- I see, you are thinking it is going to require you to give confidence intervals, et cetera.

DR. SIMON: Previously it sounded like the regulations are requiring to determine -- that the study be adequate and well-controlled enough to determine that the drug product has an effect on the surrogate endpoint, not that you can adequately define the response rate.

DR. TEMPLE: Well, for purposes of this, the first question asked is this an adequate and well-controlled study from which you can learn anything, and then the next question asks you what it has shown. If it is not a well-controlled study, you cannot learn anything from it.

DR. WILLIAMS: It is the wording about response, Dr. Temple. It is the fact that it says, you know, if you determine a response rate, you have to determine there have been certain confidence intervals, and the question is can you reword it in some way. You just want to say evaluate response, or something like that.

DR. DUTCHER: Do you want to say for the purpose of determining reasonable clinical benefit? How do you want to word it, Dr. Simon?

DR. SIMON: I would word it the way the regulations say, to determine that this has an effect on the surrogate endpoint.

DR. TEMPLE: Well, that is a second level question. That is the result of the study. The first question was intended to see if you thought it was a study in which a result would be meaningful. For example, if you thought that follow-up was awful, then you could not learn anything.

DR. DUTCHER: You have to stop at the first line on that question.

DR. WILLIAMS: How about for just evaluating response? Would that be okay?

DR. TEMPLE: Sometimes you have what looks like a very well-designed study, and it shows that one therapy is better than another, but the p-value for it is .13. So you might say this looks like an adequate and well-controlled study, but then you reach the conclusion I cannot learn about this. Our law is written that way. It says that you must assess effectiveness through adequate and well-controlled studies, and then it says the results of those studies must be convincing to experts. It breaks it down in that logic. First, do we have a trial we can work with here? For example, the control group might be wrong. Then it is not a relevant study. You do not have to ask what it

shows, because it could not show anything. So we commonly break it down into is this a study from which one can learn anything. For example, if you were very upset by the failure to get central pathology, you would say, no, I cannot learn anything from this.

DR. SIMON: [Comment off-mike.]

DR. TEMPLE: Because legally it has to be an adequate and well-controlled study. That is the only thing you can learn from.

DR. SIMON: [Comment off-mike.]

DR. WILLIAMS: For evaluating response, how about that? I think determining is such a strong word, from a statistical standpoint. How about evaluating? Would that be more appropriate? Or estimating. That would be a good way.

DR. KROOK: My comment on this question would be that I am comfortable until I get with the two arms, because I do not think -- I think what has been shown is that in an adequate trial, we have shown that people can respond from ara-C that is given in some form, but I do not -- I mean, we cannot compare one with the other. There is not enough information. So I have a problem with the last five words here, with DepoCyt versus.

DR. DUTCHER: How about is study DTC 92-001 an adequate and well-controlled study for the purpose of

evaluating response in lymphomatous meningitis?

DR. WILLIAMS: Well, that would probably be okay, since we are asking it in the next question, Dr. Temple.

DR. TEMPLE: Well, you have certainly accepted as a basis for approval so-called phase 2 studies in oncology where there is no comparator at all. So you can be a well-controlled study without a comparator. At least in oncology you can. So you could reach the conclusion just as you said that this is good enough to establish a response rate. You might even find that the presence of the ara-C makes it a little more credible, even if you do not love that comparison.

DR. KROOK: Well, I do not, but I think if I heard the sponsor, what they said was there are no controlled trials in the literature of a group of patients. This is probably the largest trial to be published in lymphomatous meningitis, with cytologic response and the rest.

DR. TEMPLE: Could you say a little more about why you do not find the comparison persuasive or of interest or any of those things?

DR. KROOK: Well, I think you have, as you look at what was presented by Helgi here, you have so many variables. You have some which have more CNS lymphoma. You have some that receive treatment. I think it is just too small. That is my problem.

DR. TEMPLE: Even for the endpoint of CSF response? I mean, if this were a mortality study, I could understand that and say, oh, how do we know -- you are now just talking about clearing the CSF. Is that as much of a problem even for those?

DR. KROOK: No, it is that I think that the arms are -- I mean, the number of patients in both arms are extremely small and it took them a long time, and you have so many variables. You can see obvious responses in both arms, and as it gets farther down, I do not see any great harm -- I think that you are seeing responses in both arms, and in this disease most of us would accept stable. Not always do we accept stable as a response. Here I think we would, in the disease.

DR. DUTCHER: I think you could argue some of the missing data as either a positive or a negative. I mean, that is the dilemma. I mean if you say one had an accidental positive cytology at not the initial site and so that one is no longer a responder because they were positive again, and then you had a couple of accidental negatives because you did not tap them, I mean, you are making too many assumptions of either positives or negatives, and I think you just have to deal with each group as a separate group and say you have cytological response from this agent.

DR. TEMPLE: Just to be clear, that is not because

the study is too small. That is because some data that was supposed to be collected was not collected. Those are two different things, aren't they?

DR. SIMON: Well, I think there clearly is some uncertainty as to whether we can say from this study that DepoCyt is clearly superior to ara-C with regard to complete cytologic response rate. That was not the original intent of the study, and not only because of the sample size but because of conflicts of interpreting response rate, limitations some of which are inherent in treating very sick patients and doing studies on very sick patients, we do not have conclusive evidence as to whether DepoCyt is superior to ara-C with regard to that surrogate endpoint.

But I think we do have evidence that DepoCyt, that there is a trend in that direction. I think there is a sense -- we have already voted -- that that endpoint is a reasonable surrogate endpoint, but I do not think we can draw conclusive comparative conclusions, and it does not exactly sound like we need to in terms of satisfying the requirements for accelerated approval.

DR. TEMPLE: You do not, but you need to say a little more about what you find impressive. Just for example, if you take scenario 1, you got three responses. If you take scenario 2, you have seven, but that requires that you accept some peripheral-read slides. Somewhere in

there something must persuade you that you got responses, and we would just like to know what that is. I am not arguing the point at all. I am just trying to get you to say what it is that makes you feel good about it. I understand that failure to follow up the other sites in the ara-C group makes the comparison with that group much weaker, because those might have been responses. So I understand your reservations about why you are not quite ready to say it is superior, but do I read from you that you are not that worried about the lack of central reading? Because that is what takes you from three to seven. Otherwise you only got three responses, pretty light.

I do not want to put words in your mouth. I want to understand what you are saying.

DR. DUTCHER: Well, I guess I am not so worried about the lack of central review. I mean, I am surprised that there was that much of a discrepancy, because some of these places do a lot CSF looking. So I am just wondering how subjective it was and whether they had lymphoma markers on the cells versus just histology. I mean, there are a lot of different reasons. So I would like to know more about that, which I do not think we are going to find out, as well as beta 2, a few other markers in the CSF which we do not have access to.

DR. OZOLS: We know from the previous review that

about 23 percent of the time, I guess, you have some changes on central review. So that is one out of four. Again, maybe one of those patients would have been changed.

DR. WILLIAMS: Our estimate would be between one and two, because one of the patients was the atypical, which there was 50 percent upgrade by the central review. So we would estimate between one and two.

DR. SCHILSKY: I guess the thing that I have been most persuaded by from the data we have seen today is that plain old ara-C is pretty poor therapy for this group of patients, and as I have been trying to point out, it is not clear to me by any scenario, by any definition of response, that DepoCyt is any worse than plain old ara-C, and it is conceivable to me that it could be better, but I do not think the data are sufficient to allow us to make a judgment about whether it is better. So I think in my own mind, maybe we will get a little ahead of the discussion here, but in my own mind the fact that ara-C seems to be pretty poor therapy, the fact that DepoCyt is not clearly worse and certainly easier to give, I think those things really should cause us to think about the value of having this therapy available.

DR. TEMPLE: I have to say if all you can tell us is that it is not worse and that the control does not work, we will end up turning it down. You might want to go to the

strongest conclusions that can be drawn from the data we have, but there needs to be a conclusion reached for us to approve it, that effectiveness as CSF clearing has been established. Now that does not mean it has to be better than the other guy, but --

DR. SCHILSKY: Oh, I am persuaded that it can clear the CSF in some patients. I am not persuaded it is better than the other, but I am not persuaded it is worse.

DR. KROVASIK: From a patient's perspective, I think with regard to this DepoCyt, I would suggest using it or making it available, marketable, just because there is not a whole lot out there, and you have dying patients. So give them a choice. I mean, we are a democratic society.

DR. TEMPLE: I am not unsympathetic to that, but that would be an illegal act on our part, and we will not do that. We have to reach a conclusion. There is obviously a great deal of flexibility in how we reach that conclusion. I mean, we are not trying to fool anybody here. But we have to reach the conclusion that it is effective, and we also have to reach the conclusion that a well-controlled study has shown that. I am not saying you cannot reach that conclusion. I just want to hear from you why you do. These things have precedent-setting qualities, and it is important that the reasoning be clear.

DR. KROVASIK: Right, I understand. I am just

coming from the standpoint of as a patient but also somebody out of the clinical trials industry, and I think given what I have seen, I think this is appropriate at this stage for limited approval, maybe doing some more studies as it progresses, but given that there is really nothing else out there and ara-C is probably comparable if a little bit less effective that what we have seen here.

DR. MARGOLIN: [Comment off-mike.] And if you decide to take the biggest numbers, which are the intents to treat, or the smallest numbers, which are the evaluable patients, or some average in between, they barely even come close to the usual, you know, two stage rule for phase 2 studies where you need one responder in fourteen to rule out a 20 percent response rate with 95 percent level of confidence. So if you look at an eight or ten patient sample, we have not even seen that plain old ara-C is so lousy. I do not think we really know what plain old ara-C does.

DR. DUTCHER: Getting back to the central review and a little bit out of order, but were any of the CSF samples tested for surface markers, or was it just purely cytology?

DR. HOWELL: The central review was done entirely on cytology alone.

DR. DUTCHER: So really up to the pathologist.

Okay, back to question number 2. The wording: is study DTC 92-001 an adequate and well-controlled study for the purpose of evaluating response in lymphomatous meningitis, which assumes that we accept the evaluation of response.

Well, do we know? Do we want to vote? Do we have to vote?

[Laughter.]

All those who would vote yes on this question, raise their hand.

[Show of hands.]

Four.

I have a no from Ms. Beaman and a no from the other patient representative. Those that would vote no?

Four no, four yes.

DR. TEMPLE: Sorry, do you understand the patient representative's vote of no after a fairly strong yes statement just a moment ago? She is gone, but --

PARTICIPANT: Both of them wrote no.

DR. DUTCHER: Question 3. One's view of the response rates obtained with DepoCyt and with ara-C will depend upon what compromises one is willing to make in applying protocol criteria for determining response; potentially acceptable interpretations of the intent to treat response rate range from 18 percent to 41 percent,

with FDA preferred analysis 18 percent versus 6 percent for ara-C. Do the response rates for DepoCyt and ara-C in study DTC 92-001 establish that DepoCyt provides a meaningful advantage over existing treatment?

DR. WILLIAMS: I was listening to the sponsor's argument regarding schedule, and it seems reasonable to include more than response rates if you would like. Do response rates and other factors, I guess, and/or other factors -- I guess we need response rates in there, because it is our surrogate.

DR. TEMPLE: Well, I think we would have to conclude that the response rates are shown to be meaningful, but there are possible advantages of the therapy that could be important.

DR. WILLIAMS: We could put and/or, but the understanding is that response rates are the basis for efficacy. So and/or other factors such as schedule.

DR. TEMPLE: So could we now clarify that or --

DR. DUTCHER: No, we have clarified that, but could we change establish to suggest?

DR. WILLIAMS: I do not think we could do that. Suggest is not strong enough for the regs.

DR. KROOK: I think you have to define what existing treatments are. I think that if you look at what the sponsor presented, they had trouble getting how many

people to agree to treatment. I do not know whether they have it, but what we have all tried to do is ask how many they went to and refused treatment, but there is a fair number of people with this disease who never get treated, particularly carcinoma, lymphoma also.

So I think you have to a little bit define existing treatment as the will of whatever somebody wants to put in there at the time, if they want to be treated. So I guess you have to define what existing treatment is, and I do not think we have a reasonable existing treatment.

My second comment is a little bit what this study may do if it is published is set up that cytologic response. Most of us struggle with what in these patient populations, when do you say they are better? When do you say they are worse. If 2 cytologic means they are better, well, that is at least better than I am doing now, except subjective. So I do not think there is a good existing treatment. We all dabble.

DR. TEMPLE: We should add one other thing, that the definition of established therapy or available therapy in that section of the regulations has become something of an interpretation problem. We do not have anything approved for this use at all in this disease, and we are currently agonizing about what available therapy means. Does it mean something we have approved? That is the FDA arrogant point

of view. Or something that people are using and think are fine. That is the more global point of view. We have not actually pinned that down, but I would say that if there is not anything approved, that goes some way towards saying that anything that appears to work has some credibility in saying that you are better than available therapy. But we have not absolutely pinned that down yet.

DR. WILLIAMS: And the fact that you have a control arm, I mean obviously if you do not think it is more advantageous than the control arm, then you could not say yes to this question.

DR. KROOK: One of the existing treatments may be our best supportive treatment. We have trouble doing that in this country.

DR. JUSTICE: My reading of the reg is that established is not required in this particular question. So if you want to modify it, you can. Established was concerning the surrogate. The surrogate is established, but the effect is not necessarily established.

DR. DUTCHER: How about support?

Okay, do the response rates and other factors for DepoCyt and ara-C in study DTC 92-001 provide support that DepoCyt provides a meaningful advantage over existing treatment in lymphomatous meningitis? Is that okay?

All right, all those who would vote yes for this?

[Show of hands.]

Six, and one more yes from the patient representative. So seven yes, and a no vote for Ms. Beaman. Seven yes, and I guess we would just put her as not available.

Okay, all right and then the last question. In the two studies of intrathecal treatment with DepoCyt, the DepoCyt arm experienced more toxicity than the control arms, methotrexate and ara-C respectively. In the study comparing intrathecal DepoCyt to intrathecal methotrexate in patients with carcinomatous meningitis, 11 patients on the DepoCyt arm were hospitalized with symptoms suggesting chemical arachnoiditis compared to 2 patients on the methotrexate arm. In study 92-001, headache and nausea and vomiting were more common on the DepoCyt arm than on the ara-C arm.

Now, that was clarified, was it not?

DR. WILLIAMS: Right, and if you want the actual words, you can turn to page 5 of the FDA review where it is actually quoted from the sponsor's previous NDA. So apparently it is an integrated summary that would have included other numbers. Perhaps if you want to provide the n's for these values, the number of patients?

DR. HOWELL: There is only one hospitalization in the DepoCyt lymphoma study in which the hospitalization occurred in association with symptoms that could be

construed as arachnoiditis. That hospitalization was not because of.

DR. WILLIAMS: Right, well, I am reading from -- there were two separate --

DR. HOWELL: The integrated summary report that you are reporting from includes the total of five studies.

DR. WILLIAMS: Okay, how many patients?

DR. HOWELL: It is 105 patients.

DR. WILLIAMS: One hundred and five DepoCyt and how many methotrexate?

DR. HOWELL: About 27.

DR. WILLIAMS: About 27. So there were 11 versus 1.

DR. HOWELL: Those also include the phase 1 trial in which the dose was being pushed up to a much higher level.

DR. DUTCHER: So the 11 patients reflect five different studies. All right.

We have had a pretty lengthy discussion about arachnoiditis headache and whatever. I think we have a pretty good feel for the extent of those problems.

Considering the balance of efficacy and toxicity demonstrated in these trials, does the committee recommend accelerated approval of DepoCyt for intrathecal treatment of lymphomatous meningitis?

All those who would vote yes?

[Show of hands.]

Five, and a yes from the patient representative. Six yes.

No?

[Show of hands.]

One no, and one not here.

That is it. Any comments?

[No response.]

All right, well, thank you all for succinct presentations of a lot of tough data.

See you in January.

[Whereupon, at 5:20 p.m., the meeting was concluded.]