UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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DIVISION OF ONCOLOGY DRUG PRODUCTS

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54TH MEETING

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FRIDAY,

SEPTEMBER 19, 1997

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The meeting took place in Versailles Ballrooms I and II, Holiday Inn Hotel-Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland at 8:30 a.m., Janice J. Dutcher, M.D., Chairman, presiding.

PRESENT:

JANICE J. DUTCHER, M.D.	Chairman
JANNETTE O'NEILL-GONZALEZ	Executive Secretary
DAVID H. JOHNSON, M.D.	Member
JAMES KROOK, M.D.	Member
KIM A. MARGOLIN, M.D.	Member

ROBERT OZOLS, M.D., Ph.D.	Member
RICHARD L. SCHILSKY, M.D.	Member
SANDRA SWAIN, M.D.	Member
DONALD W. NORTH FELT, M.D., F.A.C.P.	Guest Expert
DAVID M. ABOULAFIA, M.D.	Guest Expert
MICHAEL MARCO, B.A.	Patient Representative
DESMAR WALKES, M.D.	Consumer Representativ e
ROBERT DELAP, M.D.,Ph.D.	FDA Representative
JOHN JOHNSON, M.D.	FDA Representative
ROBERT JUSTICE, M.D.	FDA Representative
KEN KOBAYASHI, M.D.	FDA Representative
ROBERT TEMPLE, M.D.	FDA Representative
SAMUEL BRODER, M.D.	Sponsor Representative
KEN DUTCHIN, Ph.D.	Sponsor Representative
PARKASH GILL, M.D.	Sponsor Representative
GREGORY HARRIMAN, M.D.	Sponsor Representative
JOHN HOWES, Ph.D.	Sponsor Representative
GREGORY HARRIMAN, M.D.	Sponsor Representative
JOHN HOWES, M.D.	Sponsor Representative
MICHAEL BETTS	Patient Perspective
STEVEN CAROL	Patient Perspective
ERIC FLETCHER	Patient Perspective
GAVIN GRAY	Patient Perspective
DAVID GREEN	Patient Perspective

JIM MOLINA	Patient Perspective
WILLIAM W. LI, M.D.	Public Comment

ALSO PRESENT :

STEVE CARRIER, Ph.D.

T-A-B-L-E O-F C-O-N-T-E-N-T-S

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

8:47 a.m.

CHAIRPERSON DUTCHER: We are not going to get started for about five more minutes. We are waiting for some handouts. So feel free to get another cup of coffee.

[Pause.]

CHAIRPERSON DUTCHER: Good morning. This is the Oncology Drug Advisory Committee meeting. My name is Janice Dutcher. I'm an oncologist at Albert Einstein Cancer Center in New York and I'd like to have the members of the committee introduce themselves and where they are from. We can start at this end, please.

DR. WALKES: My name is Desmar Walkes. I'm a family practitioner from Bastrop, Texas and the consumer rep substituting on the committee.

DR. OZOLS: Bob Ozols, medical oncologist from Fox Chase Cancer Center in Philadelphia.

DR. SWAIN: Sandra Swain, medical oncologist, Washington, D.C.

DR. SCHILSKY: Rich Schilsky, medical oncologist, University of Chicago.

LT. O'NEILL-GONZALEZ: Jannette O'Neill-Gonzalez, Executive Secretary for FDA and for the

committee.

DR. JOHNSON: I'm David Johnson, medical oncologist at Vanderbilt University.

DR. SIMON: I'm Richard Simon, biostatistician, National Cancer Institute.

DR. MARGOLIN: Kim Margolin, medical oncologist, City of Hope, Duarte, California.

DR. ABOULAFIA: Dave Aboulafia, medical oncologist and hematologist, Virginia Mason Clinic, Seattle, Washington.

DR. NORTHFELT: Don Northfelt, I'm a needs oncologist at University of California, San Diego and Pacific Oaks Medical Group.

DR. MARCO: I'm Michael Marco, Director of Opportunistic Diseases for the Treatment Action Group, New York.

DR. KROOK: Jim Krook, medical oncologist, Duluth, Minnesota.

DR. DELAP: Bob DeLap, Oncology Drug Division Director, FDA.

DR. JOHNSON: John Johnson, Clinical Team Leader, FDA.

DR. KOBAYASHI: Ken Kobayashi, Medical Officer, FDA.

DR. TEMPLE: Bob Temple, Director of

Office of Drug Evaluation I.

LT. O'NEILL-GONZALEZ: Good morning. I'm going to be reading the Conflict of Interest Statement.

The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of a conflict. Based on this Committee's agenda and information provided by the participants, the Agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. 208(b)(3), full waivers have been granted to Dr. Sandra Swain and Dr. Kim Margolin. A copy of this waiver statement may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12830 of the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Ozols and his employer, the Fox Chase Cancer Center, have interests in Bristol-Myers Squibb and Pharmacia Upjohn, sponsors of competing products to Paxene which do not constitute financial

interest in the particular matter within the meaning of 18 U.S.C. 208.

Notwithstanding these interests, it has been determined that it is in the Agency's best interests to have Dr. Ozols participate fully in all matters concerning Ivax's Paxene.

With respect to FDA's invited guests, Dr. Donald Northfelt has reported interest which we believe should be made public to allow the participants to objectively evaluate his comments. Dr. Northfelt would like to disclose that in 1996 he received consulting and speakers fees from Sequus Pharmaceuticals.

In the event that the discussion involves any other 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 financial involvement with any firm whose products they might wish to comment on. Thank you.

CHAIRPERSON DUTCHER: Let me just

reiterate, as we discussed yesterday, we will have an open public hearing at this point in the meeting. In addition, additional time has been added to the sponsor's time for patients whom they would like to have speak on behalf of their drug to come forward. So that will be later in the morning.

But for right now, we will have the open public hearing and Dr. Li has asked to speak. Please identify yourself and your constituency.

DR. LI: Lieutenant O'Neill-Gonzales, Dr. Dutcher, members of the Committee. Good morning and thank you for the opportunity to come here to speak.

I'm Dr. William Li, medical director of the Angiogenesis Foundation, a 501(c)(3) non-profit organization whose mission is to coordinate global efforts in bringing about angiogenesis-based therapies. Today I've come to this Oncologic Drugs Advisory Committee meeting on Paxene or paclitaxel, to direct the Committee's attention to the angiogenesis inhibitory activity of paclitaxel, a property which we believe is under recognized. The Committee should consider that Paxene's antiangiogenic effects may contribute to its cytotoxic effect on tumor cells.

Paclitaxel is an effective cancer chemotherapeutic agent that has been used to treat

refractory ovarian cancer, metastatic breast cancer, advanced head and neck cancer, non-small cell lung cancer, and malignant melanoma. Several clinical trials suggest its effectiveness in regressing AIDS-associated Kaposi's sarcoma.

Paclitaxel has unique mechanisms of action. The mechanism commonly cited is its binding to the beta two subunit of tubulin. This prevents depolymerization and promotes stabilization of microtubules. Because of this, paclitaxel inhibits mitotic spindle formation, the G2 and M phase of the cell cycle, cell proliferation, cell motility and chemotaxis. This mechanism is thought to be directly responsible for paclitaxel's anticancer effects.

There is, however, another mechanism by which paclitaxel inhibits tumor growth. Paclitaxel also inhibits angiogenesis, the process of new blood vessel formation.

Solid tumor growth is dependent upon angiogenesis. Without a new blood supply, tumors are restricted to a small size, less than two millimeters in diameter. Once angiogenesis is initiated by tumor cells, new vessels bring in oxygen, nutrients and survival factors that allow for exponential tumor growth, invasion and metastases. The concept of

antiangiogenesis, first proposed in the early '70s, is designed to inhibit this process and it's a new therapeutic modality being developed by pharmaceutical companies worldwide, and by the National Cancer Institute. We believe that paclitaxel's antiangiogenic activity also contributes to its anti-tumor activity.

Paclitaxel inhibits angiogenesis by at least three mechanisms. It inhibits endothelial cell proliferation. It inhibits endothelial cell locomotion. And it inhibits protease production by endothelial cells, including the production of collagenase, which is involved in dissolving the extracellular matrix surrounding growing new blood vessels.

Paclitaxel inhibits angiogenesis in experimental systems such as the chicken chorioallantoic membrane and in vitro cultures of capillary endothelial cells. Studies by Ernest Brahn at UCLA also show that paclitaxel can inhibit angiogenesis in an animal model of collagen-induced arthritis. In companies like Bristol-Myers Squibb and Angiotech Inc. have specifically referred to antiangiogenesis as one activity of paclitaxel.

How might this information influence the

Committee's views of Paxene?

First, Paxene's antiangiogenic activity lends validity to its rationale for treating Kaposi's sarcoma. KS lesions are highly angiogenic, composed of vascular-like spindle cells and they secrete at least six angiogenic cytokines, including basic fitroblast growth factor, vascular endothelial cell growth factor, platelet-derived growth factor, interleukin-6, transforming growth factor beta, GM-CSF, and also the HIV-Tat protein. Therefore, antiangiogenesis is a rational approach to treating KS.

Second, because of its antiangiogenic activity, Paxene may have promise for treating other angiogenesis-dependent diseases, including rheumatoid arthritis, diabetic retinopathy, psoriasis, and solid tumors. Further studies need to be conducted. Until such studies are completed, we believe that appropriate cautions for the off-label use of Paxene should be developed.

Third, there may be valuable lessons to be learned from other angiogenesis-inhibitor drugs in the clinic, such as TNP-470, thalidomide, marimastat, and interferon-alpha. With these drugs, we are learning that long-term therapy is needed for efficacy. The

optimal biological dose may be lower than the maximal tolerated dose. And, that the detection of angiogenic cytokines in blood, urine and cerebrospinal fluid may serve as useful surrogate markers to monitor therapy.

Fourth, if approval is given, during the post-marketing surveillance period for Paxene, we encourage physicians to be alert for possible unanticipated, beneficial anti angiogenic effects such as the inhibition or stabilization of diabetic retinopathy or improvement in psoriasis in those Paxene treated AIDS patients with these co-morbid conditions.

There may also be unanticipated adverse effects due to antiangiogenesis such as the inhibition of collateral formation in coronary artery disease or the delay of wound healing after surgery.

In summary, we wish to emphasize to the Committee that Paxene's effects include the inhibition of angiogenesis. This lends validity to its use for treating Kaposi's sarcoma, opens up new avenues and potential applications of this drug, and it shows that this drug merits further specific examination for its effects as an antiangiogenic agent.

Thank you.

CHAIRPERSON DUTCHER: Thank you very much.

Is there anyone else in the audience who wishes to speak at the open public hearing at this time? [No response.]

Then we are going to move ahead with the applicant's presentation and I believe we have some handouts at this time. I hope. Okay.

This is a discussion of NDA 20-826, Paxene indicated for failure of first line or subsequent systemic chemotherapy for the treatment of advanced AIDS-related Kaposi's sarcoma. Dr. John Howes is going to begin the presentation.

DR. HOWES: Ladies and gentlemen, members of ODAC, good morning. I'm John Howes with the Regulatory Affairs Department of Baker-Norton Pharmaceuticals. Today we will present data to support the use of Paxene for the treatment of advanced AIDS related Kaposi's sarcoma in patients who failed first line and subsequent systemic chemotherapy.

Regrettably, Dr. Jerome Groopman, who was scheduled to be the opening speaker, is unable to attend the meeting today. In his place on the agenda will be Dr. Samuel Broder, Senior Vice President for Research and Development at Ivax Baker-Norton Corporation.

Since we do have a rather full agenda today, I will now pass the podium to Dr. Broder.

DR. BRODER: Thank you very much. Kaposi's sarcoma is an angioproliferative tumor characterized historically by endothelial and spindle cell proliferation, angiogenesis, inflammatory cell infiltration, and edema. In 1994, a new herpes virus, HHV-8 or KSHV, was discovered and found to be closely associated with this tumor and may play a role in its pathogenesis.

This tumor is one of the hallmarks of AIDS. Slide 1 please. The inter-relationship between immunodeficiency diseases and cancer generally, and between AIDS and Kaposi's sarcoma specifically, has been a very high priority of the National Cancer Institute and its viral cancer programs.

Clinical research done at the Institute suggested that Kaposi's sarcoma is sensitive to paclitaxel, a natural product originally derived from the pacific yew. This line of work is an extension of about 30 years of research on paclitaxel by the National Cancer Institute.

Next slide please. Paclitaxel, of course, has effects on tubulin and the state of tubulin polymerization. But perhaps even more interesting, as

we heard in part, are newly described mechanisms of action for this agent. Paclitaxel inhibits angiogenesis and induces apoptosis by Bcl-2 phosphorylation triggered by Raf-1 activation. It is possible that these new mechanisms may be induced by lower plasma concentrations of paclitaxel than the effects on the microtubule system.

AIDS-related Kaposi's sarcoma frequently can be an aggressive disease, often with extensive cutaneous lesions, but also involvement of the oral cavity and visceral organs. AID-related KS can be complicated by lymphedema. Could I have the next slide please? And this may involve the extremities, the face or the genitalia.

Gastro-intestinal lesions may cause bleeding, pain and obstruction and pulmonary lesions may be associated with respiratory insufficiency or death. Even in the absence of symptomatic visceral disease or edema, Kaposi's sarcoma may have a serious impact on quality of life by causing disfigurements and social isolation or by serving as a visual reminder of an AIDS diagnosis.

When Kaposi's sarcoma lesions can be covered or obscured by clothing, a patient's recognition that lesions are growing progressing is

still a serious medical challenge.

Next slide please. Although milder forms of Kaposi's sarcoma in the context of AIDS with slow progression or without life threatening visceral involvement can be treated with local or intralesional therapies, the more serious, advanced forms, if left untreated, do not spontaneously resolve as a general rule, and require cytotoxic chemotherapy.

We believe that Kaposi's sarcoma and the therapeutic challenges that this disease forces upon us will remain an important problem, notwithstanding the formidable advances that have been made in treating retro-viral diseases.

As is true in virtually all of oncology, the status of prior chemotherapy is an important consideration. Efficacy results with patients naive to chemotherapy should generally not be pooled with results in second or third-line therapy.

Since the early 1990s, the ABV regimen, which consists of dixorubicin, bleomycin and vincristine, has been considered the standard of care. In evaluating individuals or in making comparisons between clinical trials, it is important to know whether the patients have been previously treated with doxorubicin. Moreover, in the past two years,

liposomal anthracyclines have been introduced, but for a variety of reasons, it is important not to lump these two therapies together indiscriminately.

Next slide please. DaunoXome, that is liposomal daunorubicin, was approved as first-line treatment based on a prospective randomized trial comparing DaunoXome to ABV. Although response rates were similar, 23 percent for DaunoXome and 30 percent for ABV, there was significantly less alopecia and neuropathy in the setting of DaunoXome.

Next slide please. Doxil, that is liposomal doxorubicin, was approved as second-line treatment of advanced AIDS Kaposi's sarcoma based on a 27 percent response rate in 34 evaluable patients.

By contrast, the response rates reported for paclitaxel, some of which we will discuss later, for second-line treatment of Kaposi's sarcoma have been higher. And this was in part discussed at the Advisory Committee immediately preceding this current meeting in the June ODAC meeting.

For safety purposes, it is probably wise to use all available patients. But paclitaxel is not an exception to the rule that for efficacy purposes it is important not to pool first and second-line patient data.

Also, because of the non-linearity of paclitaxel pharmacokinetics, caution is in order when one extrapolates from one dosing level or apparent dose-intensity to another. We will touch upon these points in our presentation.

Next slide please. We believe that Paxene makes an important contribution to the knowledge base for paclitaxel in second-line AIDS related Kaposi's sarcoma. Our study included advanced patients who frequently had failed second-line or third-line treatments. Specifically, many of the patients were Doxil failures.

Another major point is that the study presented today is the first prospective multicenter study of paclitaxel in advanced Kaposi's sarcoma, and as such may give a more realistic estimate of community based results.

We will also touch upon the concept that perhaps in this tumor more than most there is an element of observer's subjectivity in making determinations of response.

We will also provide important information on pharmacokinetics as well as information on co-administration with protease inhibitors. We believe the latter is a very important set of information in

that now there is a nearly universal use of this category of antiretroviral agent.

We believe that much of the information that will be presented today is unavailable in any other form. For prescribers it is important to have as much empirical data as possible on both the positive features and the limitation of paclitaxel.

Finally, we wish to thank the Chair and the FDA and the members of this Committee for permitting some of the patients who participated in this study to speak here today at the conclusion of our scientific presentation.

All clinical progress depends on the willingness and courage of patients to enter studies on the safety and efficacy of new drugs.

Members of the Committee, members of the audience, thank you very much. I now would like to turn the podium over to Dr. Gill who is the principal investigator of this study and he will provide some of the data related to efficacy results. Dr. Gill.

DR. GILL: Good morning. Can you go to the next slide. This Paxene study was conducted in patients with advanced Kaposi's sarcoma. It was a prospective phase II trial in patients who had failed prior systemic cytotoxic chemotherapy. The trial was

conducted in nine U.S. sites and patients were enrolled between January '96 and April of '97.

Patients were eligible for this trial if they had advanced disease defined by one or more of the following criterias: multiple cutaneous lesions, presence of visceral disease or symptomatic lymphoedema. Other eligible criterias included failure of prior cytotoxic chemotherapy. Patients were required to have KPS of 60 or above. And the use of concomitant antiretroviral agents, including protease inhibitors, were allowed.

Primary study end points included best response and time to progression. And secondary end points were change in symptom distress scale and Karnofsky performance status. Paxene Pharmacokinetics were also performed in a subset of the patients and these data will be presented by Dr. Ken Duchin.

The response criteria used in this trial were those defined and used by ACTG-Oncology committee for the past several years. Complete and partial responses were required to be maintained for at least 28 days.

The treatment regimen consisted of Paxene given at a dose of 100 milligram per meter squared over three hours every two weeks after premedication

with dexamethasone, cemetidine and diphenhydramine . One does reduction was allowed to 75 milligrams for toxicity. In the event of more severe toxicity, treatment was withheld until recovery. Use of G-CSF for treatment of neutropenia was also permitted.

Eighty nine patients were enrolled in these nine sites through April of 1997 and two large accrual regents represent Boston and Los Angeles.

The patient demographics are outlined here. The median CD4 count was low at 40 and a majority of the patients had Karnofsky performance status between 70 and 80, 61 percent.

Antiretroviral therapy was taken by 71 percent of the patients at study entry, this included use of protease inhibitors in 33 patients. In addition, a third of the patients were receiving therapy for CMV infection and 30 percent of the patients were receiving G-CSF.

The tumor assessment at baseline showed mucocutaneous disease in all but two patients, facial disease in 42 patients, and oral disease in 40 percent. Tumor associated edema was also observed in nearly half of the patients and visceral disease was present in 42 percent. Pulmonary involvement was the most common site of visceral involvement.

TIS staging system has been developed for prognostic prediction for this disease and this accounts for three different areas, tumor burden, immune status and systemic illness. Poor prognostic features for these include tumor associated edema, visceral involvement and extensive oral disease, immune status of CD-4 being less than 200 and the prior symptoms of opportunistic infections and the past history of these symptoms of low performance status.

Next slide please. Utilizing these TIS staging criteria, in this study two or more of these poor prognostic features were present in 90 percent of the cases.

All patients had received prior cytotoxic chemotherapy. Over a third of the patients had received two or three prior cytotoxic chemotherapy regimens. Among these patients, 46 percent had received liposomal daunorubicin and 30 percent had received liposomal doxorubicin.

A median of eight cycles of Paxene was administered with a range of one to 27. Thirty four patients remain on study after receiving ten cycles of therapy. The median dose intensity in this trial was 44 milligram per meter squared per week.

Response rates were assessed by intent to treat analysis. Complete and partial responses were observed in 46 percent with 95 percent confidence interval of 41 to 62. These data represent the independent review by Dr. Kaplan who was not an investigator in this trial.

This is a representative example of responding patients. A patient with advanced cutaneous disease and extensive edema which was associated with pain and required use of crutches showed marked improvement after 19 cycles.

Looking at the impact of prior therapy and outcome, patients who received one prior regimen had a response rate of 47 percent compared to 41 percent for those who received two or three prior regimens.

The response rates in those who received prior liposomal daunorubicin or liposomal doxorubicin were 51 percent and 33 percent respectively.

The impact of protease inhibitor use was also examined. Twenty nine patients did not receive any protease inhibitors during the trial. The response rate of 41 percent in this subgroup compared to the overall response rate of 46 percent suggests that protease inhibitors may not have a significant impact on the possibility or probability of response

outcome.

The median time to response in this patient population was 49 days. And the duration of response which was calculated from initiation of treatment has not been reached and would be in excess of 306 days.

Time to treatment failure for the study population was 234 days.

I would now ask Dr. Harriman from Baker-Norton to conduct the remainder of the presentation. Thank you.

DR. HARRIMAN: Thank you, Dr. Gill. Good morning ladies and gentlemen, members of ODAC and guests. My name is Gregory Harriman and I'm with Baker-Norton Pharmaceuticals. Before beginning my presentation, I would like to have Dr. Ken Duchin from Baker-Norton get up and give a brief presentation of the pharmacokinetic studies.

DR. DUCHIN: Good morning. Thank you very much. We present data today on the pharmacokinetics of paclitaxel in AIDS KS patients in the study just described by Dr. Gill. It must be recognized that these studies were very difficult to conduct given the demands on the patients' time and we are very grateful to the patients who participated in this

pharmacokinetic study.

Eleven patients from one site volunteered for pharmacokinetic sampling. These patients were taking four to 20 concomitant medications, which included one or more reverse transcriptase inhibitors, imidazole antifungal and the protease inhibitor indinavir. The protease inhibitors are of particular interest because paclitaxel and protease inhibitors are metabolized by cytochrome P453A and almost all of the marketed protease inhibitors carry a warning in their product label of potential interactions with concomitant medications that also utilize this metabolic pathway.

Serial plasma sampling, which involved about 20 samples per patient, occurred over 51 hours during and after the three hour infusion of Paxene on one of the cycles.

Nine patients were studied on one cycle and two patients were studied twice on two consecutive cycles.

The next slide shows the mean plasma concentration time curve for paclitaxel in the nine patients who were studied on one cycle.

Mean pharmacokinetic parameters are shown in this slide. I wish to point out that peak plasma

concentrations (Cmax) averaged 1100 nanogram per mil or about 1.3 micromole and body clearance averaged approximately 27 liters per hour per meter squared.

A comparison of some of the pharmacokinetic parameters obtained at the dose of 100 milligrams per meter squared was made using a weighted analysis to values obtained from other Paxene studies in 37 patients with solid tumors who received a higher dose, 175 milligram per meter squared.

As noted on the left hand side of the slide, a 75 percent increase in administered dose was accompanied by much greater increases in peak plasma paclitaxel levels and in areas under the curve to the last detectable concentration and to infinity. The dash line would be the expected increase in these parameters if the drug obeyed linear kinetics. These data demonstrate the nonlinearity of the pharmacokinetics of paclitaxel over the range of 100 to 175 milligram per meter squared.

We also evaluated the pharmacokinetics of Paxene in those patients taking indinavir and those who did not. As noted here, there were no differences in the average values for Cmax, body clearance, lima distribution or elimination half life between these two groups.

In another two patients, paclitaxel kinetics were obtained on two consecutive cycles, one in the absence of indinavir and the second after two weeks of indinavir therapy. As shown here, the plasma levels of paclitaxel were similar with and without indinavir, confirming that indinavir does not alter the disposition of paclitaxel.

Imidazole antifungal agents are known to inhibit cytrochrom P450 enzymes and it was of interest to assess whether those patients taking imidazole antifungal, primarily fluconazole, had greater exposure to paclitaxel.

On this slide it is clear that there was no indication that patients taking antifungal had higher Cmax values or reduced clearance values compared to those not taking these drugs.

In conclusion, these studies define for the first time the pharmacokinetics of paclitaxel in AIDS KS patients taking multiple HIV therapies. Paclitaxel displays nonlinear pharmacokinetics over the range of 100 to 175 milligram per meter squared when administered over three hours and there was no appreciable interaction between paclitaxel and indinavir or the imidazole antifungal agents. Thank you.

Now I would like to ask Dr. Harriman to come back to the podium.

DR. HARRIMAN: First, I would like to summarize study results relating to quality of life and patient benefit. Then I will review the safety results, including the safety of Paxene in patients on protease inhibitors. Finally, I will provide some conclusions regarding the efficacy of Paxene in the treatment of patients with advanced AIDS KS who have failed prior cytotoxic chemotherapy.

In this context, failed refers to patients who progressed on or were intolerant of the chemotherapy. In many cases, these patients have failed more than one cytotoxic chemotherapy regimen, including Doxil. Such patients are an important group for whom the identification of effective treatment can be challenging.

Quality of life was assessed by a prospectively-obtained patient-administered Symptom Distress Scale as well as by Karnofsky Performance Status and photographs. The Symptom Distress Scale contains 15 questions related to overall well-being, for example, outlook, concentration and fatigue; as well as disease-related symptoms, for example, appearance, pain, mobility and breathing.

Each question uses a five-point Likert-type format in which a score of one is the best possible score, meaning no distress, and a score of five is the worst possible score, meaning severe distress. The Symptom Distress Scale was to be administered at baseline and every third cycle. Internal consistency and test-retest reliability estimates have indicated the scale is reliable and the scale has been previously validated.

Karnofsky Performance Status was to be assessed at baseline and each cycle. Photographs of marker lesions and other involved areas were to be obtained at baseline and every six weeks.

Shown here is the median total score of all 15 questions for patients at baseline and cycles four, seven and ten. There was a highly statistically significant improvement in the median score at cycles four, seven and ten. Very few patients were lost between baseline and cycle four, indicating that the improvement seen at cycle four, at least, is unlikely due to bias.

Assessment of tumor responses can be difficult and open to a certain amount of interpretation, as Dr. Broder mentioned before. Thus, it is possible for a patient to not be scored as

having a tumor response, despite having clear evidence of clinical benefit.

Shown here is a patient previously treated with Doxil. He had extensive involvement of his foot with tumor and a large ulcer. The patient was informed that he might have to have his foot amputated. Following treatment with Paxene, the patient had a very significant improvement in the tumor and ulcer on his foot. This patient was not scored as having a tumor response in this protocol, although he clearly benefitted from his treatment. This patient and others are with us today and they hope to have an opportunity to tell us about their experience with Paxene.

This patient had extensive lesions of his gums. He also had a very severe lesion on his chest. While there were some differences of opinion as to whether he was a responder, he clearly has had improvement in his disease.

Shown here are median scores in patients with facial lesions for questions relating to the patients appearance at baseline and cycles four, seven and ten. There was a statistically significant improvement in this score at cycles four, seven and ten. Again, few patients were lost between baseline

and cycle four, indicating that the improvement at cycle four, at least, was unlikely due to bias.

As can be seen, this patient had severe disfiguring lesions and edema on his face. With treatment, he had a marked improvement in the lesions and edema.

This slide shows improvement in symptoms such as pain and mobility related to lymphedema. Again, there was a statistically significant improvement in these symptoms at cycle four. While improvement continued at cycles seven and ten, it was no longer statistically significant.

This patient had marked lymphedema in his right leg which responded well to treatment, with maintained improvement to cycle 13 as shown here.

This patient had severely crusted lesions with significant lymphedema in his left lower extremity. The lymphedema showed definite improvement at cycle three of treatment.

This slide shows improvement in symptoms related to pulmonary disease which include breathing and cough. A statistically significant improvement in the median score was seen at cycles four and seven. Although a similar magnitude of improvement was seen at cycle ten, this was not statistically significant.

This patient had severe pulmonary involvement and had previously been treated with both DaunoXome and Doxil. Of note, he was on oxygen prior to treatment, but was able to discontinue this treatment following the Paxene treatment.

This patient also had pulmonary involvement. At cycle 13 of treatment, pulmonary lesions were significant improved, as demonstrated by a decrease in one of the pulmonary lesions seen on this cut of the CT scan. Free study and cycle 13.

Forty-six percent of patients had improvement in their Karnofsky Performance Status during treatment. The improvement seen was statistically significant. The majority of remaining patients had no change in their Karnofsky status and a few patients had worsening.

Thus, improvement in quality of life was seen in patients treated with Paxene as judged by improvement in symptoms, by Karnofsky Performance Status and by photographic improvement.

With regard to safety, frequent hematologic and non-hematologic adverse event occurring in the 89 patients are summarized here. The major toxicities were hematologic, including neutropenia and anemia. Other frequently occurring

adverse events included asthenia, alopecia, nausea and/or vomiting, arthralgis and myalgias, peripheral neuropathy and rash.

Adverse events were also analyzed by whether or not patients were on protease inhibitors as shown on this slide. There was little difference in the incidence of adverse events between the two groups of patients and none of the differences were statistically significant.

There were a total of 70 opportunistic infections in 30 patients during study representing 34 percent of patients. Of these opportunistic infections, 17 which involved mycobacteria, pneumocystic, cryptococcus and CMV would be considered serious.

There were 11 deaths which occurred while patients were on study. Of these 11 deaths, the investigators felt four were related to Paxene. Three of these patients of sepsis with associated neutropenia and one patient died of congestive heart failure due to pulmonary hypertension.

We also have substantial safety data with Paxene using different doses and schedules in patients who have other forms of cancer. Shown here are adverse events, which were included in the NDA, on not

only AIDS-KS patients, but an additional 226 patients who received Paxene at either 140 milligrams per meter squared over 96 hours or 175 milligrams per meter squared over three hours. Again, the major toxicities were hematologic.

Next slide. However, alopecia, arthralgia/myalgia and peripheral neuropathy were also fairly common, although severe grades of these toxicities were not common. Hypersensitivity reactions were also relatively uncommon. We currently have safety data on a total of over 500 patients.

In summary, while AIDS-KS patients are potentially at increased risk because of their underlying disease and multiple concomitant medications, no unusual or unexpected toxicities were observed in AIDS-KS patients treated with Paxene.

Now, I would like to summarize the data which has been presented by responding to the questions which were addressed by FDA to ODAC. First, Is the Paxene study size of 89 patients adequate for approval of a drug for the use after failure of first line or subsequent systemic chemotherapy for the treatment of AIDS-related Kaposi's sarcoma?

To answer this question, this study must be put into perspective with respect to studies which

lead to the approval of other drugs for similar indications. As discussed, the study reported here was a prospective, multicenter study enrolling 89 patients, with two geographically distinct sites, Los Angeles and Boston, enrolling 25 or more patients each. It should be kept in mind that all 89 patients had failed prior cytotoxic chemotherapy and many failed two or more cytotoxic chemotherapies. Thus, these patients, by and large, represent a very refractory population.

In looking at the study sizes for other drugs currently approved for second-line treatment of AIDS-KS, there were two studies which were the basis upon which Taxol was approved for this indication. One study, which looked at dose and schedule of 135 milligrams per meter squared every three weeks, enrolled 29 patients. However, only 19 of these patients had received prior systemic therapy, of which only seven evaluable patients had received cytotoxic chemotherapy. Moreover, only four of these had received an anthracycline.

The second Taxol study used a dose and schedule of 100 milligrams per meter squared every two weeks. In this study, 56 patients were enrolled. However, only 40 of these patients had received prior

systemic chemotherapy.

The approval of Doxil for second-line therapy in AIDS-KS was based on 77 patients who had received prior combination chemotherapy. However, only 34 of these patients were felt by the FDA to be evaluable.

Thus, the Paxene study containing 89 patients and representing a refractory population of patients, is larger than any other study used to support approval of a drug for second-line or subsequent treatment of advanced AIDS-KS.

Next slide. The second question was, "Does the Paxene study show patient benefit based on the 42 percent cutaneous tumor response rate, the clinical benefits assessments and the quality of life assessments?"

As previously discussed, the overall tumor response rate with Paxene was 46 percent. Patients had advanced AIDS-KS as demonstrated by the large number of patients with disfiguring lesions, tumor related edema and visceral disease. In addition, the vast majority of these patients were poor risk by TIS staging. Moreover, as mentioned previously, these patients were a very refractory population with respect to prior cytotoxic chemotherapy.

Thus, the 46 percent tumor response rate should be viewed as highly significant. The fact that patients had substantial response rates, even after failing Doxil, which until August 4th of this year was the only approved drug for second-line treatment of advanced AIDS-KS and the significant response rates in patients who have failed two or more prior cytotoxic therapies, should be viewed as evidence of substantial activity.

Time to progression and duration of response with Paxene were also substantial given this patient population.

Moreover, patients demonstrated improvement in quality of life based upon significant improvement in total Symptom Distress Scale scores, as well as improvement in symptoms related to facial lesions, lymphedema and pulmonary disease. This is the first time that a prospective quality of life assessment containing such a Symptom Distress Scale has been used in AIDS-KS patients. Significant improvements were also seen in Karnofsky Performance Status and evidence of improvement was documented by photographs.

In sum, the combination of high tumor response rates, as well as improvements in quality of

life measurements, provide substantial evidence in support of patient benefit.

The third question, "Is the Paxene safety acceptable in view of the efficacy results and results available with alternative therapy?"

Efficacy results were just discussed. With regard to safety, this slide shows the most important or most common adverse events with Paxene in comparison to adverse events reported in AIDS-KS patients treated with Taxol and Doxil. The point here is that Paxene exhibited no higher incidences of any of the toxicities seen with Taxol and in some cases the rate may be lower.

As discussed earlier, in this study a substantial amount of safety experience was gained with the coadministration of protease inhibitors and Paxene. No significant differences were seen in the rates of major or common adverse events in these two groups of patients. Furthermore, pharmacokinetic studies were performed to assess the effects of protease inhibitors on the pharmacokinetics of paclitaxel.

Thus, while Paxene has some significant toxicities, as expected with this cytotoxic drug, it's safety is no worse and in certain adverse events may

be better than Taxol, which is currently approved for second-line treatment of AIDS-KS.

The fourth question, "Is the Paxene ND A approvable for the indication of use after failure of first-line or subsequent systemic chemotherapy for th e treatment of advanced AID-related Kaposi's sarcoma?

Paxene demonstrates a high tum or response rate in patients, all of whom have failed at least on e or more cytotoxic chemotherapies. Moreover, the tumo r response rate is similar to that of Taxol when used a t the same dose and schedule of 100 milligrams per mete r square d every two weeks and is higher than that o f Doxil.

Importantly, Paxene demonstrate s substantial tumor response rat es even in patients who have failed Doxil. In contrast, only one patien t previously receiving Doxil was treated with Taxol in registration-seeking studies.

In conclusion, Paxene induces tumo r responses as defined by ACTG criteria in 46 percent o f patients with advanced AIDS-re lated KS who had failed first-line or subsequent systemic chemotherapy . Paxene improves quality of life, as assessed by a Symptom Distress Scale and Karnofsky Performanc e Status. Paxene is also safe in the treatment of AIDS -

related KS.

Paxene induces tumor responses in 33 percent of patients who have failed prior Doxil therapy and 41 percent in patients who received at least two prior cytotoxic chemotherapies. Paxene is safe and effective in patients on concomitant protease inhibitors.

The proposed indication is Paxene is indicated after failure of first-line or subsequent chemotherapy, including liposomal doxorubicin, in patients with advanced AIDS-related Kaposi's sarcoma, and for relief of disease-related symptoms. Coadministration with protease inhibitors does not diminish the efficacy or alter the side effect profile of Paxene.

I would now like to provide an opportunity for some of the patients who have been treated with Paxene to come up and share their experiences with you. Thank you very much.

MR. FLETCHER: Good morning, ladies and gentlemen. My name is Eric Fletcher. I am not being financially rewarded for being here today. I'm here out of a heartfelt concern.

Since I was 15 years old, I have worked as a fashion model. This allowed me to move away from

home at 17 to support myself through college and to pay for it and I was a taxpaying citizen where I contributed to society in general. This was until two years ago.

In the fall of 1995, I was diagnosed with AIDS. More devastating was the fact that I had Kaposi's sarcoma, KS. After an endoscopy to show that the KS was rampant throughout my insides, after a couple of weeks lesions began to appear all over my body.

My world began to collapse. I was 30 years old. I relied on my physical appearance as the basis of my existence. This was my means of livelihood. Why was I being tortured? I had been completely healthy all my life. I was a vegetarian. I didn't smoke. I never did drugs or alcohol and I was not promiscuous. I wanted to know why this was happening to me.

My doctors immediately started me on chemotherapy. This scared me because I had seen the faces of people on chemo and in my experience those people didn't have a long chance of survival. Reluctantly, I started a clinical trial of Donozone. I was concerned about hair loss, but I was assured that this would not be a side effect. This made a

vain man happy.

I remained on the study for about six months. I experienced nausea, vomiting, sleep loss, loss of appetite, subsequent weight loss and a host of other problems. My heart infraction rate became too low. I couldn't tolerate the drug any longer. Early in 1996 I had to stop treatments.

My doctors decided to start me on ABV. I was told that I would definitely experience hair loss. Around this time I started to experience edema, my features grew beyond recognition, my lesions grew worse. They became open ulcers and wounds. I needed my bandages cleaned and changed three times daily.

I went from 170 pounds down to 125 pounds. I couldn't walk. I used a wheelchair because I didn't have the strength to move, or to bathe, or to even go to the toilet. Obviously the ABV wasn't working.

Needless to say, I gave up hope. I reached a low in my life I had never known. I considered suicide. I asked my primary care provider about assisted suicide. I started to give away my life souvenirs and treasures. I prepared myself and my loved ones for me death, or they prepared me. They were so tired of seeing me suffer that they said that if God was ready and if I wanted to, that I could give

up.

My hopes, my dreams were all gone. I considered myself a monster. I couldn't look at myself in the mirror. KS had taken away my pride, my dignity.

In all my misery, however, the one thing that I didn't lose was my spirit. My soul is good and joyously in all my darkness I attracted many wonderful people into my life. Many doctors, nurses and the support system.

One of those doctors highly recommended that I try this new protocol. I had no choice. It was either Paxene, ICU or death. At this point, what was there to lose? My hair?

I started Paxene in June of 1996 along with a triple antiretroviral protease inhibitor therapy. I cut my hair really short so I wouldn't see it fall out. Surprisingly, my hair never fell out. In actuality, I never experienced any side effects.

My doctors told me I wouldn't see the effects of the triple therapy for about three months to a year. However, after my first cycle of Paxene, I began to see and feel a positive difference.

I am now up to my 30th cycle. Treatments are every two weeks. My lesions have faded. Many are

barely noticeable. My ulcers have healed. I have regained all my weight, plus some. I have regained -- I have my normal energy level. I am even running three miles a day.

More remarkably, my appearance has improved so greatly that I am back to work as a fashion model headed for a career in television.

Now, here is my plea. Paxene is not political with me. Nor is it a miracle drug. It is simply my life. It may not be a cure for this dreaded disease, but it makes life a whole lot more manageable. It has given me the ability to once again look in the mirror to see what's really there, a person full of life and love and has given me the ability to share that joy.

I hope you will immediately approve Paxene so many other people will have a chance to once again have dignity and self worth. But more importantly, as only a person who has seen the face of death will ever know, the true miracle of this drug is its ability to allow one to appreciate every moment that they once again have been granted and to lead a more fulfilling and rewarding life.

I greatly urge you to immediately approve Paxene for the treatment of KS. A small company like

Baker-Norton cannot survive another couple of years, therefore they will have to discontinue operations and I will no longer have the drug. Ultimately, the promise of my future will be taken away again. Thank you.

MR. CAROL: Good morning. My name is Steve Carol and I'm here today at the invitation of Baker-Norton Pharmaceuticals. Although I am being compensated for my expenses, I am here today to invite you to share in my enthusiasm about a discovery I happened upon during this past year.

My wife and I were devastated when I was diagnosed with Kaposi's sarcoma in 1993. Further tests confirmed that I was HIV positive. At that time, my doctors followed the approved therapy for KS which began with radiation treatments. Although tolerable, the therapy did little more than slow the progress of the disease.

After that treatment came injections of interferon and interlukin 2. Again, that provided to do little to improve my situation. Next came the systemic chemotherapy treatments beginning with ABV, three drugs that were used in different combinations but with limited success. I had little tolerance to the drugs and would have to discontinue the use of

them after two or three cycles of each combination.

Next came my participation in several studies involving the use of liposomal chemotherapies, including Doxil and Donozone. Once again, my intolerance to the long-term use of the drugs caused my doctors to discontinue any further treatments.

By this time my weight had dropped from 200 pounds to about 128. My hair was just beginning to return after having been lost to the chemotherapies. Up to this time, my skin lesions had been confined to my feet, legs and arms. But now I had several facial lesions that were drawing much attention.

Another lesion had ulcerated on the bottom of my foot and had left a very painful opening about the size of a quarter that you could place your little finger into up to the first joint. This left me for a year and a half either on crutches or confined to a wheelchair and unable to work.

My doctors told me that there was nothing more that they could do for me and that the only thing left to consider was the amputation of my right leg. This was not a measure that would stop the cancer, but would end the every day threat of infection to a wound that would not heal.

The ulcer was very large and ominous. My wife could not bear to look at it, even from across the room. Special nurses had to come to my home to clean and treat the wound on a daily basis. A one-legged man was sent to our home to talk to us about life after amputation.

Not being the kind of person that gives up easily, I found out about Dr. Seville and the study he was conducting at the University of California-San Diego of a new treatment for KS. Although skeptical, I became part of the study and began treatment in December of 1996.

After several cycles I noticed a number of things. First of all, I didn't feel sick to my stomach all the time. The lesions on my face were disappearing and the wound on the bottom of my foot had begun to improve.

I had none of the intolerance to the treatments that I had previously experienced, and for the first time in years, I began to feel good about myself. I no longer woke up angry every morning just because I woke up. I no longer felt helpless against something that was slowly taking my life. And although there was some hair loss again, I thought that was a small price to pay for something that was

obviously working so well.

I can now report to you that I walk without the use of a cane or crutches and there have been no new lesions to report for many months. The tumors that I do have are greatly diminished. And I went back to work last month.

I and the others that are appearing before you today represent not only ourselves, but thousands of others who suffer from this disease. We depend on governing bodies such as yourself to help advance the use of such life saving drugs as Paxene and allow us to enjoy the same quality of life that each of you enjoy every day.

I am here today to ask you to grant approval to the use of Paxene in the treatment of KS. Thank you.

MR. GREEN: Good morning. My name is David Green and I am a 47 year old executive chef. I tested positive for HIV in 1982 and remained asymptomatic until January of '94 at which time I found my first KS lesion on my lower back. In four months, I had six lesions on my body.

At the time I was living in San Diego and the doctors there said they were not aggressively treating KS unless it was presenting a serious

problem. Mine were not as yet.

Over the next year, I developed many more lesions over my torso. In June of '95, several of the lesions became raised and three of them had started to weep. I still had no treatment.

By October '95, the dressings on the weeping lesions had to be changed at least three times a day. The lesions were becoming quite tender. I also noticed at this time a slight discoloration on the tip of my nose and a swollen spot on my upper gum.

At Scribbs Clinic in San Diego, I saw an infectious disease specialist who sent me for consultations with both radiation and hematology, oncology departments. At that time a lesion was also found on my lung.

The recommendation was radiation to slow the growth in my mouth and wait and see on the rest. Also, perhaps I should consider moving back to Boston to be with my family and to get my affairs in order.

It took three months to wrap things up in San Diego and get to Boston. In that time the lesions in my mouth grew quite rapidly. Now both my upper and lower gums had turned purple and had grown to completely cover my teeth. My hard palate had also grown and the only way I could eat was to put very

small pieces of food in my mouth and try to swallow. It was painful.

Another lesion the size of a marble appeared under my right ear and I was now getting short of breath without much exertion.

On arrival in Boston, I was referred to Dr. David Skadden at Mass General Hospital. He told me I had a few options. We decided that I would first try Doxil. It had just been approved and he felt that it was the least toxic and a good place to start.

After only two treatments, the pain was gone and after six I started to notice some changes in the lesions. They were shrinking. At about three months into treatment I could see the tips of my teeth. The weeping lesions on my torso were beginning to dry up.

Slow progress continued until June of '96 when I had a breakthrough. One of the lesions on my right thigh had flattened and become -- which had flattened became raised again. It also became quite tender. The lesion on the tip of my nose began to darken as well. However, from the time I started treatment, I had developed no new lesions.

It was at this point that Dr. Skadden and I decided I should try -- should join the clinical

trial for Paxene. With only one treatment, the raised lesion was again flat and with two the tip of my nose lightened. I really looked forward to going to treatments.

The treatments themselves are very easy to tolerate. The worst part is the length of time you spend in the chair. The side effects are minimal. I lost body hair, eyebrows and eyelashes. I do need nupegen to keep my white count out but the dosage has been reduced. The other side effects, hiccups, constipation and heartburn are not due directly to the Paxene, but rather the decadeon I'm given as a premed, and they are easily taken care of.

I feel so well these days that after receiving treatment I walk a mile and a half to the Boston Living Center where I volunteer. I continue to receive Paxene every two weeks for a year. My mouth is now normal. I still have teeth and most importantly, my sense of taste is still acute. The lesions on my torso are flat and dry and fading. My lungs are clear.

In July '97, I went on a three week cycle with continued fading of the lesions. I am now on a four week cycle and the lesions continue to fade.

I never thought that I would feel or look

so healthy again. There are not enough good things that can be said about Paxene. It's a drug which I believe should be made available to everyone.

MR. MOLINA: Hello. My name is Jim Molina. I am not being compensated for being here today. Baker-Norton Pharmaceuticals has paid for my ticket since I was unable to afford one on my own.

I was diagnosed HIV positive on April 19, 1993. Upon my diagnosis, I asked the doctor if the spot on my left shin had anything to do with the HIV. "Oh, it looks like a little KS, nothing to be alarmed about. We'll just monitor it and see if it changes" he replied.

Not knowing what KS was, I figured the doctor knew what was best for me, so I went along with his advice. Later a chest x-ray was requested by my doctor. The x-ray revealed a quarter size lesion in the lower left lung and a cat scan was ordered. This revealed the same results as the x-ray. Next I had a bronchoscopy. The test was inconclusive as the doctor was unable to get to the area of my lung that was in question.

So the next move was to try a fine needle biopsy or to remove the lower half left of my lung -- the lower left half of my lung. I was uncomfortable

with the invasiveness involved in both of these procedures, so I chose to monitor the lesion regularly.

Time passed to about March of 1994. It was then that my doctor had pointed out some enlarged lymph nodes on my neck that I had thought had been there forever. My doctor insisted on a biopsy of the lymph node. The biopsy revealed that I had Kaposi's sarcoma in my lymphatic system on April 4, 1994. This news was devastating. I knew what cancer was, but I did not know anybody who had KS. I was still dealing with the HIV diagnosis and trying to come up with a way to break the HIV news to my mother.

I was hit with both barrels. I had so much to do. I thought I was going to die and I had to come clean with my mother who had already lost her only other child in an alcohol-related accident. Let me tell you that was one of the most difficult things I ever had to do.

I am so fortunate to have the support of my mother and my lover Phil. I don't know how I would have come through all of this without them. Little did I know that was just the tip of the iceberg compared to the battle ahead.

Within a period of about six months, my KS

had begun to spread. Slowly at first, then all of a sudden it went rampant. I watched as my body changed. First there were only visible lesions. Then I noticed my ankles were beginning to swell, then my legs, then I couldn't squat anymore.

Now during all these changes the doctors at Kaiser were going through the routine with the available drug therapies. On September 13, 1995, my oncologist prescribed interferon which I had no response to. The only thing it did for me was make me feel like I had the flu after each injection. That lasted for about two months. So my oncologist wanted to try radiation on my groin and upper thighs.

I was under the impression the radiation was helping as my skin began to fall the new skin was unscarred. Little did I know the radiation also damaging my lymphatic system in my groin area. This was obviously not the answer since swelling in my feet and ankles began to increase with each day.

Then in December of 1995 the oncologist tried etopacide which was quickly added to the list of options that were not working. And then vincristine, vinblastine. As time passed, it was March of 1996 and my doctors at Kaiser had to inform me that there were no other alternatives. They had done all they could

for me at Kaiser. What a cold day that was for me.

I was suffering, swollen and b eginning to lose all use of my legs. I can't even describe to yo u the mental state that I was in. I still had yet t o meet another person who was going through this. I began to hide from the public, so aware of my lesions and their ugliness. I was ready to give up. I becam e obsessed with my death and how it was going to happen and at that time I feared death. I was left to lay o n the couch in constant pain, just waiting, waiting to die.

I had a lot of time to think and in m y thinking I began to pray for the strength to get m e through each day and the guidance to get me to someon e who could help me or even relate to this new disease that was changing me in so many ways.

Then on April 15, 1996, my prayers wer e answered. The latest addition of Positive Living had an article on the cover about KS. This was the first instance where I saw anything related specifically to Kaposi's sarcoma. I read furiously and found myself in the clinical trial section which I had never paid attention to before. And then I realized that I had everything to lose by not opening my eyes to th e alternatives.

I found only one trial that I thought I was qualified for since I was in such an advanced stage. So I called and spoke with Miki Ilaw Jacobson. She seemed so interested in meeting me. I was happy to have someone respond to me in such a positive way.

Miki told me that all of the other drugs I had tried -- they had tried and rejected, were nothing in comparison to the current trial for Paxene. She was confident that she could help me and I felt I could trust her from the beginning.

I met Miki the following day and I will never forget that day. Miki had restored my hope in living. I had to wait two weeks before I could start treatment and those two weeks proved to be the most challenging. It seemed like the KS knew what was coming. I began to swell up and the new lesions were coming faster than I thought possible. It was like a game of beat the clock getting to infusion day.

By the time May 8th arrived, my day of infusion, I had begun to give up. I was so depressed I was pushing the people in my life away to prepare for my death. It must have taken me 45 minutes to get myself from my car to the clinic. I could barely walk and I had to rest often on that endless journey to the clinic. But I finally made it and I received my first

infusion with this new drug, Paxene.

The next day after the infusion, I was amazed. I woke to legs that were relieved of much of the pain and for the first time in a long time my legs had reduced in size. I could even see the veins in my feet. I was so happy. I called everyone I knew and I told them of my progress. And so far with each subsequent infusion, I continue to get better.

There have been times when other circumstances have prevented me from getting my infusion. Every time this occurred, the KS began to bloom again proving to me that I need this therapy continuously.

I am so happy to say that I'm feeling better than I have in over a year. The combination of Paxene and the new antivirals I am on have changed my once losing battle to a battle worth fighting. I know now that I am no longer alone.

My suffering has changed to a will to fight back. Paxene has given me time to reopen relationships with those I once pushed away and I have been given a second chance to live.

For me the side effects have been minimal. I began to lose most of my hair, but suddenly it grew back with a vengeance. I began to have severe

heartburn after infusion, but we've learned that it can be controlled with prozac. I also get the hiccups after infusion, but that I can deal with myself.

I would like to thank Baker-Norton, Dr. Parkash Gill and Miki Ilaw Jacobson for their support and all they have done for me to help me in my fight against KS. I honestly believe that without them and my loved ones, I would not be here today to offer my testimonial.

So I and my family urge you to approve Paxene, not only for use in people with KS but for their loved ones as well. Thank you.

CHAIRPERSON DUTCHER: Thank you. We certainly do appreciate the input from the patients. You must release this was on the time that was allotted to Baker-Norton. How many more speakers do you have? Because you have reached your time limit. One more?

[Brief discussion off mike.]

CHAIRPERSON DUTCHER: Can we finish in five minutes? Okay.

MR. GRAY: Good morning. I have prepared quite an extensive presentation, but I will make it short. My name is Gavin Douglas Gray and I am here, and my expenses are being paid by Baker-Norton

Pharmaceuticals.

In December of 1992, I had a medical examination and went back to find out that I was in fact HIV positive. I dealt with the situation as best as I could and as one best can given the facts.

A year and a half later I was diagnosed with AIDS-related Kaposi's sarcoma and was forced to quit my job and go on disability and began receiving chemotherapy treatments with ABV which failed me after a couple of months. I went on to interferon and failed on that and went on to Doxil and remained on that for about six months. After 48 treatments of Doxil, my KS condition advanced to an even more malignant stage and I was at that point 25 pounds underweight, emotionally depleted with very little hope and as many others have said, just looking to my death as the last solution to my situation.

I was put on Donozone and I did not respond to that, and I heard about Paxene through a friend whom I did not recognize at the time because he looked so wonderful. He looked like a whole new person.

I went on to try Paxene reluctantly because what else was I going to do? Try it or be done with it. I had an incredible response to Paxene.

My lesions started to disappear. The pain went away. I was able to eat again and started to get my level of energy back to normal and today you are looking at a completely different man than I was prior to Paxene.

I ask all of you that if this drug has brought me back from the edge of my grave, then it should also be allowed to help many others who cannot make it to a parochial study, who are in rural areas of this country that should be receiving it. Approval of it is a must for them. It's in your hands to restore hope and to give back the life that many of those people once had like I once did.

I am grateful for this drug. I highly recommend it. And it's much, much more tolerable than any of the other drugs that I tried. And it works unlike any of the others. Thank you.

MR. BETTS: Hello. My name is Michael Betts. I'm a California resident currently receiving Paxene treatment in combination with protease inhibitor treatment. My travel expenses have been paid for by Baker-Norton Pharmaceuticals Inc. That's the only compensation that I am receiving.

I am here today to urge your approval of Paxene as a chemotherapy treatment against Kaposi's sarcoma and last year around this time I was actually

planning a funeral. I wasn't sure I was going to make it. But I feel much better now.

To my knowledge, I've been HIV positive for approximately seven years and in April 1996, after noticing an irregular swelling in my right ankle, I was diagnosed with KS. Between the months of April and July of 1996, the swelling increased from being just my ankle to my entire right leg. I am a fairly active person. I run and exercise quite a bit. And I was really disturbed by this reduction in my personal mobility.

Along with the swelling caused by the lymphedema, I had no energy, I had heat that kind of emanated from my leg and I had bumps that secreted an oozing pus almost constantly. I noticed that when my stress level increased or when I had an increase in physical activity during the course of the day, the swelling was more pronounced. It was painful even to wear socks.

My leg felt as though it was going to explode from the pressure and it felt like it was filling up with a fluid that was just going to burst out of me at some point.

I was bloated most of the time and uncomfortable. And on one occasion, my leg enlarged

so much during the course of the day that I couldn't take my pants and my boots off . I had to go to sleep that way until my leg went down. I had a lot of difficulty bending at both my knee and my ankle.

During the same period, my skin became blotched and the swelling was noticeable through my clothing. The evidence of my conspicuous appearance and medical condition made me feel depressed and reclusive. I remember one really important event. I went to the supermarket one day and a woman and her child followed me through the entire market trying to guess what kind of affliction I had, what was causing my leg to be so big that they could notice it through my clothes. And it caused me to isolate myself.

I was so isolated and withdrawn that I completely stopped attending family functions. I stopped doing anything that required being in public. And my neighbors gave me the nickname the "vampire" because I only did things at night.

There is a level of humor I think you have to retain in order to survive an illness and its treatment. But when my body started to change against my will, it was devastating. I had lost control. I had to question whether I could walk to the store, whether I'd wear short pants, whether I could take the

stairs and the insensitivity of other people. I kept a strong exterior, but I was withdrawing.

Initially, I was introduced to Donazol as a chemotherapy treatment, but it wasn't effective for me. And in November 1996, I had my first chemotherapy treatment with Paxene. Since that first treatment I've experienced minimal side effects. The side effects I had included hair loss, numbness in my toes and hands, dry mouth, hiccups, sleeplessness. But then I also get a real good burst of energy the day after, so that's great.

In contrast to the side effects, I've had Paxene therapy every two weeks for the last ten months, and have had great improvement in my condition. My leg is almost back to its normal size and I have periodic swelling only as a result of excessive exertion. The KS has not spread and I've been told that the discoloration in my skin will correct itself in time.

I'm energetic and my quality of life has greatly improved. I feel more like myself than I have in the last two years. I walk my 90 pound dog two or three times a day. I still work full time. I work out with weights and I have a shameless appetite. I

eat everything.

I have begun again to think about the future and thoughts about a job, hobbies, changing my job, hobbies and it's been great. It's true that I'm not as able bodied as I was two years ago and I hope for that, but I'm not dead either. And I would gladly accept the minimal side effects which are lessening all the time to the alternative.

I'm not so terminally ill that joy is gone. I have hope. I'm a living and breathing testament that medical strides are being made against this villain that we call HIV.

There is nothing worse than feeling like your body is at war with itself and Paxene chemotherapy had made me feel like the calvary really is coming. I strongly support the approval of the use of Paxene by the Food and Drug Administration so that its benefits can reach others in need. Thank you.

DR. HARRIMAN: We very much appreciate ODAC providing an opportunity for patients to present their stories. That concludes our presentation and we will be happy to answer any questions.

CHAIRPERSON DUTCHER: Thank you and thanks again to the patients that came to present their stories. The Committee really does appreciate your

comments and your input.

We now have time for members of the Committee to ask questions of the sponsor. Who would like to begin? Would consultants like to start? Dr. Swain?

DR. SWAIN: Could you just discuss the concomitant use of the protease inhibitors and the timing with your study and the patients and if that had any effect on responses that you saw.

DR. HARRIMAN: Right. We had 32 -- sorry, 33 patients who were on protease inhibitors at the start of their treatment with Paxene. We had a total of 62 patients who were on protease inhibitors at some time during their treatment with Paxene. Those -- the other patients, other than the 33 that were on at the start of therapy, were begun on protease inhibitors at some time during their treatment with Paxene. We had another 27 patients who were not on protease inhibitors at any time during their treatment with Paxene.

If I could have, if I could have back up slide no. 158, please. If you just look at, just break the groups down into just two -- two groups. The patients who never received protease inhibitor at any time and patients who were on protease inhibitors

at some time and look at tumor response rates, you can see -- you can see that response rates were about 57 percent in patients who were on protease inhibitors and 41 percent in patients who were not on protease inhibitors.

I'm sorry. These patients were on protease inhibitors during the entire ten cycles of treatment. So this excludes patients that were started on protease inhibitors after they were begun on the protocol. And these patients were patients that were never on protease inhibitors at any time.

So if you look at those two groups of patients, you can see that response rates were roughly comparable. And I think that suggests probably that at least in this situation, the Paxene is able to induce tumor response rates of similar magnitude regardless of whether patients were on protease inhibitors.

CHAIRPERSON DUTCHER: Could you just comment a little bit about the lymphedema response and how many patients had significant lymphedema and how responses were assessed and the response rate?

DR. HARRIMAN: Right. There were a couple of ways in which we tried to assess the effects on lymphedema. One of them I discussed earlier and that

is the improvement in symptoms related to lymphedema in which we did see, based upon the Symptom Distress Scale questionnaire, improvements, significant improvements in the patients symptoms related to that.

In addition, we had photographs. The investigators were encouraged to take photographs of the patients with lymphedema and try and document any improvements in that. We've shown you some examples of those patients. The completeness with which photographs were taken were not 100 percent so we don't have documentation in every case.

The third way in which we tried to assess improvement was by trying to get measurements of circumference of the extremities at baseline and during treatment with Paxene. The -- although we did see, in that situation, what we believed to be some evidence of improvement, there were problems with getting complete measurements on a consistent basis in the patients and we did not feel that the data was complete enough that we could present a meaningful analysis in that regard.

DR. JOHNSON: I'd like to ask you to go back to the question Dr. Swain asked regarding protease inhibitors and actually reshow the slide you just showed us. Because I want to be sure I

understand. You have a total of 50 patients on that slide.

DR. HARRIMAN: Correct.

DR. JOHNSON: You had 89 in the study.

DR. HARRIMAN: Correct.

DR. JOHNSON: So I would conclude from that 39 patients were not on protease inhibitors when they started on Paxene and at some point during the course of receiving Paxene were started on protease inhibitors.

DR. HARRIMAN: Yes.

DR. JOHNSON: You don't give us the response data of those 39 patients.

DR. HARRIMAN: Well, they were included in the previous slide as a group. But let me show -- can you go to the previous slide we showed -- 157 -- no that's not it.

DR. CARRIER: I'm Steve Carrier, Director of Biometrics at Baker-Norton. There is a little bit of a competing risk thing going on here with the protease inhibitors start date and the response date for the Paxene. The slide that you showed 21 patients who were on protease inhibitor at the beginning of the study and used protease inhibitors during the entire ten cycles of the study during which by protocol we

were determining best response, is a peer group in which we could look at response rates in the presence of protease inhibitor.

The other group of 29 did not receive any protease inhibitor during that ten cycles and so we had a fairly peer comparison of response rates in groups that had the only difference being the presence of a protease inhibitor. The additional 39 patients began protease inhibitor at some time during the study or previous to the study, but had not been on protease inhibitor the entire study.

So 33 patients began the study with protease inhibitor, but 21 of them continued throughout basically the ten cycles. Others changed, stopped, paused, had breaks, new ones began. And those are problematic as to when to -- to which group do you attribute the response? Do you attribute it to patients who respond early in Paxene and have not yet received protease inhibitor are fairly clear. But, now you are conditioning your response on having after protease inhibitor introduction on those who were unable to respond prior to the -- and there is no clear answer to that.

We have, however, attempted to -- we've had a lot of discussions internally about this as you

might guess, to look at this and so we've done some Cox regression analyses with the introduction of protease inhibitor as a time dependent co-variant in this model and we wanted to know whether or not the introduction of protease inhibitor increased or reduced the risk of an outcome variable. And those variables were:

time to response;

time to progression of the disease where us to follow-up or death without any knowledge of whether the Kaposi's sarcoma had advanced were censored as opposed to counted as events;

time to treatment failure where all loss to follow-up, all deaths, and all progressive diseases were counted as events; and

mortality survival itself.

With the results that for time to response there was no significant effect on the response rate with the introduction of a protease inhibitor relative to not having a protease inhibitor on board.

The relative risk was about two with confidence bounds of about .93 to 4.6 having protease inhibitor on board versus not having protease inhibitor on board.

For time to progressive disease, we didn't

really see a significant effect at all. The relative risk was about 1.1 with confidence bounds of .35 to 3.3. However, when we finally get to time to treatment failure, which includes the mortalities now, the relative risk is down to .43 meaning a 57 percent reduction in treatment failure with the introduction of protease inhibitor. Confidence bounds were .232 to .797 and a P value was 0.007.

And finally the mortality where I think this is consistent with everybody's expectations, the relative risk is down to .266, the P value associated with is 0.0015 and confidence bounds are 0.23 to 0.80 with the risk being reduced by the introduction of protease inhibitor or that -- over not having that protease inhibitor introduced into the patient population.

Thank you.

DR. JOHNSON: So do I understand from your Cox regression analysis, are you -- did you just tell us that the time to response was better --

DR. CARRIER: The time to response was not better. Whether you respond or not was not better. But as you begin to introduce the end points of life, the mortality itself, then the introduction of protease inhibitor reduced the risk of having the

negative end point, a prolonged life, prolonged a time to -- before treatment failure occurred.

DR. ABOULAFIA: Do you have any information about viral loads on these patients who were recruited in these studies?

DR. HARRIMAN: Yes, as part of the protocol design, viral loads were not assessed and that's primarily because the onset of the study was at a time where that was being done less routinely. We do have some sporadic measures of viral loads and if we could just show some of these. If you could go to -- okay, here is patient 856. This is his viral loads. At prestudy at cycle five and two measurements I guess at different times at cycle six.

Can we also see number 187 please. Oh, I'm sorry, here is another one, a patient whose viral loads were done at pre-study cycle nine and cycle 14. And 190, and here is another patient whose viral loads were done at cycle four, 13 and 16. So that gives you just a very sporadic information about viral loads. But again, that wasn't part of this protocol design and it was -- the protocol was undertaken primarily before these were being done routinely.

DR. ABOULAFIA: What would be interesting to know, not so much what the effect of Paxene is on

viral loads, but what the response rates are on patients who have non-detectable loads. Not using a protease inhibitor is a surrogate marker --

CHAIRPERSON DUTCHER: Use the microphone. You need to use the microphone.

DR. ABOULAFIA: Sorry. What I was saying is it would be interesting to know what the effect, not of what Paxene is on viral loads per se, but the response rates of patients who had non-detectable viral loads versus those who had poorly controlled viral loads. Do you have any kind of data like that?

DR. HARRIMAN: Given the fact that we really, as I said, have only sporadic measures of viral loads, we don't have any data that would substantively address your question. What I -- just to try and get at it indirectly though, what I would show you, if I could have slide 151 please.

One of the points to make in this is that when patients respond to Paxene, and then this is basically just a figure that's showing the percent of patients who were responders who responded at different cycles from zero through nine. And, once patients are begun on treatment, there is a fairly rapid increase in the number of responders. It turns out the median cycle of response is cycle three.

Now this is -- we feel at least some evidence to suggest, given the fact that the patients were often begun on protease inhibitors at various times during treatment, that this very rapid increase in response suggests at least that the response we are seeing is primarily an effect of the paclitaxel, the Paxene itself, rather than at least not -- at least in part due to the Paxene and not entirely due to the introduction of protease inhibitors.

Moreover, if I could have slide 159 please, this is a graph showing the rate of response in patients who were not using protease inhibitors. And again, you see a pretty rapid response here as the patient receives additional cycles.

If I could have the next slide please. And, this is a slide of patients who were using protease inhibitors and I think the two curves are fairly similar and again, I think it's indirect evidence but at least it suggests that the protease inhibitors are certainly not entirely, and we don't feel largely responsible for the responses that we are seeing.

DR. MARCO: Can I do two follow-ups on the protease inhibitor questions? One, do you have a breakdown by protease inhibitors? Somebody on hard

cap sequenivere monotherapy ve rsus somebody on triple therapy with indinavir is goin g to be different. So, if you could show us that.

And also I don't know if you really ca n answer this, but in your NDA 6.8 tumor response b y concomitant protease inhibitor use, that's a complete flip from what you are just showing now. Originally you were telling us that patients on proteas e inhibitors did worse, albeit not statisticall y significant, than patients not on protease inhibitors . What's the reason for the switch?

DR. HARRIMAN: I don't think w e ever said in any documents that we thought that patients di d worse. I think --

DR. MARCO: Not worse. I said no t signif icant. But you say the success rate of 79. 2 percent in patients not on protease inhibitors. And you say a response rate of 50 percent on patients on protease inhibitors. Even though it's no t statistically significant, the se numbers on the slide are different.

DR. HARRIMAN: Yes. Okay. Tw o points to make. One, this is again, we did not feel thos e numbers were not statistically significant. We di d not feel that they were significant.

Number two, part of the reason for the confusion, the numbers that you saw were based on an analysis that we had done prior to getting our independent confirmation by Dr. Kaplan who reviewed all 89 cases and did an assessment of tumor responses as well as cycle in which tumor responses occurred, and also the point at which progression occurred. We reanalyzed our database using only Dr. Kaplan's independent assessment of our tumor responses and timed to progression and time to response.

So the numbers that I'm showing you here today are based solely on Dr. Kaplan's analysis which I think accounts for the reasons there is a difference between that and the numbers that you see in the ODAC briefing document. The analysis that we did with Dr. Kaplan's numbers were actually done subsequent to the submission of that briefing document.

DR. MARGOLIN: I have a few questions related to the assessment of the durability of the responses and concern about long term therapy. The first one is I think it's somewhat untraditional to assess the duration of response beginning of the onset of therapy rather than at the onset of some documentation of response. But I'll just make that as a rhetorical comment because obviously the FDA has

looked at that question, I'm sure.

The question I have that I don't think was in the data you presented was you gave a median time to treatment failure, I think of 234 days. But reasons for off study -- I think it would be useful to see how many patients went off study because they relapsed among responders and/or a Kaplan Meir plot of what's happening to the responders over time. Because a duration of response not reached doesn't really tell us what's happening with at least some of these patients.

And then the related questions would be in patients who responded but who had a brief response then relapsed, do you have any data about retreatment?

DR. HARRIMAN: Okay, yes, very good questions. In terms of discontinuations, if I could have slide 128 please. These are the reasons for discontinuation, either in patients who received greater than two cycles or patients who -- greater or equal to those and patients who received less than two cycles of therapy. The 15 patients who discontinued treatment after two cycles of therapy, two were for death, two for toxicity, one for disease progression, two refused further treatment, and eight for various other reasons such as the patient moved or switched

doctors and so forth.

In patients who discontinued therapy prior to receiving two cycles of therapy, three of the patients were because of death, one was lost to follow-up, one refused further treatment and seven, again, were other, which was the various reasons that I indicated.

In terms of the Kaplan Meir, we don't have that analysis but Steve, do you want to say anything in terms of the calculation of duration to response?

[Pause.]

DR. OZOLS: I have a question about safety. You said the safety profiles in some instances may be better than Taxol. Does that relate to possible use of protease inhibitors? Do you have different toxicity profiles for use with and without the inhibitors?

DR. HARRIMAN: We feel that, first of all the two products, Taxol and Paxene, although they both contain the same active moiety, are different proprietary preparations with different formulations. Although we cannot address that specifically, it is at least a possibility that some differences in side effect profiles may be related to differences in formulation.

In terms of the possible role of protease inhibitors, I think you know, it remains I think a question that cannot really be fully answered right now. I think some of the side effects, adverse events, the difference is that we observed would seem to be at least at first blush not likely attributable to the protease inhibitors, for example, differences in arthralgia, myalgia. But I think, I really can't comment further than that.

DR. OZOLS: And then the other question in your proposed indication for failure of first-line or subsequent chemotherapy, would that include Taxol?

DR. HARRIMAN: There have been some studies that have been done, and we actually have as an amendment to our protocol in patients who progressed on three hour infusions of paclitaxel to enter them into a protocol which uses 96 hour infusions of Paxene. There were small numbers, I guess Dr. Seville in his study when he was at the National Cancer Institute, had studied small numbers of patients that had progressed on three hour infusions and found some evidence of efficacy in those patients when they were switched over to 96 hour.

As you probably are aware, also, there are studies ongoing looking at 96 hour infusions of

paclitaxel in patients who have failed three hour infusions of paclitaxel or other chemotherapy. So, I think that's a possible area that would be worth further evaluation.

DR. SCHILSKY: I've just a couple of questions. As I understand the spots criteria used in the study, it's possible for patients who have visceral disease and cutaneous disease to be scored as a response just by virtue of improvement in the cutaneous disease. And, most of the examples of response that you showed us were patients who responded with their cutaneous disease.

Can you tell us something about what the response is in visceral sites in patients who are getting this therapy?

DR. HARRIMAN: Yes. First of all, in many of the patients, although some of them had evidence of visceral disease at the time they were entered into the study and the clinicians had indicated in the case report forms that the patients had various visceral disease, in order for a patient to be followed specifically for precise specific tumor response, they had to have clear documentation, confirmation that disease was present.

For example, in pulmonary disease they

would have had to have a bronchoscopy done prior to the study and documenting KS.

DR. SCHILSKY: In your presentation you said there were 37 patients who had visceral disease.

DR. HARRIMAN: Yes. And, many of those patients that's based upon the clinical diagnosis or the clinician's impression at study entry. We had seven patients who were being followed for pulmonary disease specifically in whom attempts were made to document it, prestudy with bronchoscopies and so forth. And of those seven patients that we had confirmation of that, I believe it was five of those patients had evidence of response in their pulmonary disease.

DR. SCHILSKY: I also have a question about the pharmacokinetics. I was just curious about a couple of things. One is that other pharmacokinetics, or other PK studies of paclitaxel have suggested that the most relevant pharmaco-dynamic parameter is duration of exposure above the threshold concentration. I see that you didn't present data on that particular parameter. And I wonder if you even can generate that since the patients were only studied after 48 hours.

But it may be that the AUC and Cmax and so

on are not particularly relevant PK parameters given the way the drug seems to work . So do you have -- is there any data on duration of exposure above seven threshold concentration?

DR. HARRIMAN: Ken?

DR. DUCHIN: We didn't look at that specifically because about half the patients in the PK analysis were taking nupegen at the time. So, we felt that would confound the analysis.

DR. SCHILSKY: Why would that confound the analysis if that's what the concentrations were?

DR. DUCHIN: Because when we looked at change on the neutrophil count --

DR. SCHILSKY: I'm not asking you to relate it to any clinical parameter, I just want to know if you have data on, you know, number of days or number of hours with a concentration above the threshold value.

DR. DUCHIN: Oh, we have that, but we don't have it today.

DR. SCHILSKY: Okay. I have one other question before you go about the PK and the impact of the protease inhibitors. From the data that you showed us, it doesn't appear that there is any alteration in the PK, which, I guess, is a little bit

surprising to me. But I wonder if -- I just want to be clear that when the PK studies were done, was the only variable in a sense whether patients were getting protease inhibitors or not, or were patients also getting all of the other drugs that they were getting, plus or minus the protease inhibitors? Because it could be very difficult to sort out the PK data and try to dissect out the impact of the protease inhibitors in the presence of multiple other drugs, others of which may have an influence on various cytochrome P450s.

And so what you are looking at, I presume, is a resultant effect and it is certainly conceivable to me that effect may not actually reflect the actual impact of the protease inhibitors themselves. So do you have any sort of more pure way of looking at the data?

DR. DUCHIN: The purest way that we have are in those two patients where I presented, and clearly the only change was the addition of indinavir.

DR. SCHILSKY: So all of the other medicines that they were taking over that course of time remained constant?

DR. DUCHIN: Yes, that's correct.

DR. SCHILSKY: Okay.

CHAIRMAN DUTCHER: Dr. Northfelt?

DR. NORTHFELT: Thank you. Dr. Harriman, I noticed that in the afternoon, after the FDA evaluator makes his presentation you are not offered any opportunity to rebut. So I'd like to ask you to rebut one statement that's made in the material I read. And I just want to tell you what my bias is in this so that you know where I'm coming from.

As a clinician I don't think that the objective tumor response criteria that we are using in these studies has any real value, especially in people with very advanced disease. So I think really what we need to understand is how these treatment impact on the quality of life of these patients and what the clinical benefits are aside from the objective response criteria.

So I was very happy to see that you had done a quality of life analysis in this study and that you did show some improvements in several areas. But that was not, that enthusiasm was not shared by the reviewer from the FDA. So in part he says that results of the analyses of the SDS components and the total SDS score should be interpreted with caution due to the lack of a control group in the study. And then he goes on to say for the same reason the impact of

missing data cannot be adequately assessed, thus no claims for improvement can be validly made. And this is respect to quality of life again.

Only statements pertaining to trends toward improvement are supportable and he ends by saying the approval decision should be based only on clinical considerations of this application. So he is essentially asking us to ignore all of the quality of life information that you have presented. And I'm sort of crushed by that so I'd like you to get me back up again.

DR. HARRIMAN: Okay, I'll see if I can do that. First of all, again, I just want to emphasize that this is, to our knowledge, the first time that an attempt at taking a quality of life instrument, a Symptom Distress Scale, and studying it prospectively in advanced AIDS-KS patients with the attempt being to try and determine whether there is a feeling of improvement on the part of the patients of their symptoms.

Now, it's a fair statement to say short of a head to head randomized comparison study, one can always argue that there could be a placebo effect in other things that would bias the patient in their responses. However, with respect to that, one point

that I tried to make during my presentation and I hope it was made, but in the figures that I showed -- let me go to the one on the facial -- the point I was trying to make is that when one looks at baseline median scores and at least at cycle four where there is a highly statistically significant improvement, the difference in the number of patients -- it was 29 that had evaluations at baseline and 27 at cycle four, so very few patients were lost between baseline and cycle four in this case, although clearly patients get lost as the study goes on.

Now, I guess what I would argue is that given the fact that you had very little loss in patients between baseline and cycle four, it's hard to argue that the worst patients are dropping out and you are only looking at the better patients that are still there at cycle four. So, for that reason I think one could argue that this difference is probably real and meaningful.

About all --

DR. BRODER: We understand and deeply respect the FDA's review and we understand their comments. Our position is that we do not agree with their assessment. The prior attempts at these types of assessments have been retrospective and essentially

in effect an attempt to do quality of life assessments looking back in time, essentially after a study has been completed in many cases.

And so recognizing all of the potential limitations that one might have, I guess the simple bottom line is that this was a prospective study with statistically significant results, at least at certain parameters and at certain time points. And it must constitute an improvement over other previous attempts to make these quality of life assessments.

So with respect to the FDA on this specific point, we disagree.

DR. SIMON: I had a few questions, one on pharmacokinetics. Did you try to assess whether Paxene affected the pharmacokinetics of the protease inhibitors?

DR. DUCHIN: Yes. In one study where we had two patients that were done, we did look at indinavir levels in only a few samples. And they were within the expected range for indinavir. But we did not do a standard profile of indinavir concentrations.

DR. SIMON: Do you have data relating the objective tumor response to the symptomatic improvement on the Symptom Distress Scale for baseline to course seven? I think once you get beyond --

course four -- I think once you get beyond course four, I guess my view is there is so many patients lost from evaluation that that data and those P values are not valid. But do you have a correlation of response, objective response versus symptomatic improvement over the first four courses?

DR. HARRIMAN: Right. We had done some initial analyses in trying to correlate tumor response with improvement in the Symptom Distress Scale and, although I don't think we have that information here today with us, we did not see or rather we saw similar improvements in Symptom Distress Scale scores in patients who responded -- Steve?

DR. CAROL: The data we have is based upon our internal tumor response rate data and what we did find was that even in non-responders there was reduction in the symptom distress score, the symptomatology in that first baseline to cycle four. And we couldn't distinguish it in that period from the drop, the median change we saw in the responding group. That was by our internal assessment of response. We haven't repeated that using the independent reviewer's assessment.

DR. SIMON: One final question. You present in your application an analysis of Karnofsky

performance data over time. I guess I don't understand how that's a valid analysis given that over time, particularly these patients taking protease inhibitors, their performance is going to improve and certainly when you take their last performance score and those who go off study early because they are not responding to their HIV treatment are going to have lower -- not going to have improved performance scores and those who stay on longer because for a variety of reasons are going to have improved performance. Maybe as a result also of their anti-HIV treatment. I don't see how you can attribute that significant improvement in Karnofsky performance, how you can attribute that to treatment with Paxene?

DR. HARRIMAN: I don't -- I mean I take your point and I'm not sure we are trying to argue that the entire improvement in Karnofsky performance status is simply a consequence of treatment with Paxene.

However, I think what one can discern from that data, I think, and this is, I think, an important piece of information to gain, is that certainly the treatment with Paxene is not causing a deleterious effect on the patients' Karnofsky performance status. Moreover, notwithstanding the improvement or the

effects of -- possible effects of protease inhibitors and other variables on the results that we are seeing in Karnofsky performance status, I think in light of all of the other evidence that we have shown you, I think it's reasonable to conclude that perhaps at least some of the improvement would be attributable to the study drug.

DR. SWAIN: In the FDA document, it was stated that there is 75 percent of the patients had a one week delay and about 40 percent had a two week delay and you are recommending to give this drug every two weeks, but it seems like most of the patients really didn't receive it every two weeks. Can you comment on what's in there that there is no reason for that delay in a large number of patients and how as practitioners using this drug, it should be used?

DR. HARRIMAN: The way the protocol was designed is the patients were to have received the Paxene at two week intervals. And that was adhered to as much as possible during the first ten cycles of therapy.

It was, actually at the prompting of the investigators, their feeling was that in every two week -- after ten cycles of therapy or after the patient has responded to the Paxene, that it's very

inconvenient for the patients to come in every two week intervals to get the treatment and the hope was that one could increase the interval between cycles and still maintain responses. So we modified the protocol to allow for intervals up to three to four weeks between cycles after ten cycles of therapy. In fact, a number of patients who had completed ten cycles of therapy went to that every three or four week schedule.

We don't have any really comprehensive data in terms of being able to discuss whether patients that continue on an every two week regimen after cycle ten or those that go to every three or four weeks whether there is any difference in the time to progression or the rate of progression, because that wasn't really part of the original protocol design. But I think it's an interesting question that perhaps merits further exploration, and that is after the patient has had a tumor response, is it possible to increase the interval between cycles and still maintain responses.

DR. SWAIN: And the second question. Can you discuss the hepatotoxicity with and without the protease inhibitors that you saw?

DR. HARRIMAN: Yes. [Pause.] We don't

have that data summarized, but we can certainly get that for you. But unfortunately, we don't have it available today.

What I can say is that there was certainly no -- well, as you know patients on protease inhibitors, particularly indinavir, can have elevations in bilirubin and in some cases there appear to be a small number of patients on indinavir that can have concomitant increases in their transaminases as well as bilirubin. We did see some patients who were on indinavir who had elevated bilirubin levels, but I don't have available at this point any data that specifically compare patients that were on and off protease inhibitors with regard to that. Sorry.

DR. SCHILSKY: Could I just follow up on that for a moment because there is a substantial amount of data to suggest that patients with abnormal liver functions don't tolerate paclitaxel well and that even, you know what may be relatively trivial elevations of transaminases may predispose patients to much more severe toxicity.

So it would seem to me that in circumstances with patients who are taking a drug like indinavir which may case some hepatic toxicity that that certainly could place them at much greater risk

of Paxene toxicity if the Paxene dose is not modified. And I wonder if you thought about that and considered how you might deal with that issue in packaging labeling?

DR. HARRIMAN: Certainly the protocol specified that if patients had significant elevations in their liver function tests, bilirubin above 1.5, a five fold or higher increase in atransaminases, that that would be a criteria for dose modification of paclitaxel. We can pull up the data in terms of dose modifications. But what I can say in that regard is that is certainly a potential concern that one has to be aware of.

But again, I would just draw your attention, at least in the broad sense, to the slide I showed comparing the safety -- the adverse events of patients on protease inhibitors and not on proteas e inhibitors. At least in that broad sense we are not seeing any significant differences in terms of the toxicities. However, I agree with you, one would probably need to look very carefully at the subset of patients where there are abnormal liver function tests in order to really be able to look at that.

CHAIRMAN DUTCHER: One last question?

DR. MARGOLIN: I have actually two brief

questions that are not exactly related to each other. One is sort of generic, not pertaining only to your product, but in AIDS patients that are going to be -- excuse me, HIV positive patients who are going to be receiving this drug at two to three week intervals of what looks like prolonged periods of time.

The question is whether the risk of hypersensitivity reactions goes down sufficiently to consider tapering or perhaps even discontinuing the decadron. Because if you add up the amount of decadron that is used in these patients who are already at serious risk of OIs, it really gets to be quite a lot. And I wonder if you have data on the HSRs? I'll ask my second question after you answer that.

DR. HARRIMAN: Okay. Yes, the within the protocol there was expressed in the protocol certain doses of decadron that were to be used and its specified intervals. However, there was actually some variability in terms of both the dose of decadron that was used and the schedule for when it was given among the different investigators. And I think, I don't know whether Dr. Gill would like to talk at all about this, because I believe he has some information in that regard.

But I do think that there is at least some anecdotal evidence to suggest that as the therapy continues in patients who have not had any evidence of hypersensitivity reactions, one may be able to get by with lower doses. But to my knowledge, that's not been formally studied.

DR. MARGOLIN: The related question actually, I think Dr. Gill will end up having to answer. I'm just curious whether there was an overlap in the time frame of the accrual to this study and the other one at USC. I think I recall hearing one of the patients mention the same protocol nurse that was at the last meeting, if I'm not mistaken. The reason I ask that is because there is a question whether any selection factors or bias could have been introduced into which patients were put in which study at the same institution.

DR. GILL: Patient accrual in the first trial ended in December and this trial began accrual in January. So there is no overlap. And since I'm up I can just say that the dose on decadron has been reduced in some patients down to four milligrams, but it's never been done in an organized way to give you a sense. It seems that you can go down to four. Can you go down to zero is an important question and

hasn't been addressed.

CHAIRMAN DUTCHER: We have a couple of more questions. Dr. Aboulafia?

DR. ABOULAFIA: Thank you. Just as a quick comment. There is a point in time where patients achieve stabilization of their disease and they remain at that state. In terms of indications and how often you give this drug, you are going to have to build in the knowledge of what their HIV viral load is, and how that reflects on their case load.

And what I mean by that is not everyone needs to be maintained at two week dosing for the rest of their lives. And many of these patients who have achieved an initial response and have a concomitant reduction viral load to nondetectable levels may well be able to go off chemotherapy or really go down to much less frequent dosings.

And that's what I was trying to get at when I was asking about the viral loads or if you have data on how many different antiviral combinations patients were -- had with them when they came into the studies. Or alternatively, in the study how many times their antivirals were changed. Those are the key things.

It doesn't help me a lot to hear the data

of how many patients responded on protease inhibitors versus those that didn't if I don't have viral loads and CD4 counts to know really what their clinical state was. Many of these patients are put on viral loads, it sounds like a fairly heavily pretreated group with a CF4 count of 30. And what that means is that some of them are not going to respond to the protease inhibitors either and the fact that you are looking at groups that you had put those on doesn't mean, at least to me per se, that their viral loads are nondetectable.

DR. HARRIMAN: I'm sorry -- I didn't hear your last point.

DR. ABOULAFIA: The fact that they are on protease inhibitors doesn't allow me to infer that their viral loads are well controlled or nondetectable.

DR. HARRIMAN: Right. Yes, about all I can say in response to your question is, as we all know, the changes that occurred in the management of HIV disease over the last two years has been very dramatic and the way the current standard of care and the current way in which we approach patients with HIV is very different than it was even a year ago when this protocol, or a year and a half ago when this

protocol was begun.

I think clearly, you know, knowing a patient's viral load is going to be very important in managing the patient and also assessing the relative need for other therapies for treating their concomitant illnesses such as Kaposi's sarcoma. I don't think we can further address those questions at this time.

CHAIRMAN DUTCHER: Dr. Walkes?

DR. WALKES: You had mentioned that you allowed for one dose reduction and you had also said that the curve was not linear over 100. Is it linear below 100? And why do you have to reduce the dose? Is it because of things like hepatotoxicity? And one other thing, if you do reduce the dose, is it still effective?

DR. HARRIMAN: Those are good questions. The reason for dose reduction was for protocol specified toxicity. Primarily it was for toxicities associated with the paclitaxel, severe neutropenia, febrile neutropenia, grade the or higher hepatotoxicity or peripheral neuropathy, those types of things.

We had several patients who did have dose reductions -- yes, we had nine patients who had dose

reductions to 75 milligrams per meter squared because of toxicities. Some of those patients were able to go subsequently back up to higher doses as their Kaposi's sarcoma improved. In other cases, they stayed at 75 milligrams per meter squared.

Because of the small number of patients, we can't draw any definitive conclusions about the effectiveness of 75 milligrams except that we did have in at least a couple of cases, patients who were on 75 milligrams per meter squared and were able to maintain their response.

Okay, actually, Eric Fletcher, the first gentleman that got up to speak, had a dose reduction to 75 milligrams per meter squared. And he had a response while he was on the 75 that he subsequently more recently had gone back up to 100 milligrams per meter squared.

CHAIRMAN DUTCHER: Thank you. I think we are going to have to end the questioning right now and take a break for ten minutes. We will be back here at 11:15.

(Whereupon, the foregoing matter went off the record at 11:05 a.m. and went back on the record at 11:19 a.m.)

CHAIRMAN DUTCHER: We are now going to

begin the FDA presentation. People will take their seats please. Dr. Kobayashi?

DR. KOBAYASHI: Could I have the lights down, please? Thank you.

Dr. Dutcher, members of the Advisory Committee, Dr. Temple, my colleagues in the FDA, ladies and gentlemen, today I will be presenting the clinical portion of NDA20-826, Paxene for advanced AIDS-Kaposi's related sarcoma. Before proceeding further, I would like to acknowledge the many important contributions made by the members of the review team shown on this slide.

The indication proposed in the NDA and under discussion today is for use after failure of first-line or subsequent systemic chemotherapy for the treatment of advanced AID-related Kaposi's sarcoma. The proposed dose and schedule is 100 milligrams per meter squared intravenously over three hours every 14 days.

The primary end point of the Paxene study in this application is objective tumor response. Evidence of clinical benefit is being sought from the data on the following five domains, response of disfiguring facial and foot lesions by visual assessment, response of tumor associated edema by

visual assessment, response of pulmonary lesions and change in performance status. This in addition to cutaneous tumor response data is being presented today to obtain approval of the Paxene in this indication.

The original NDA was submitted to the FDA in June of 1994. The applicant initially proposed a 100 patient randomized controlled clinical trial in patients with AIDS-KS in July of 1995 and submitted the protocol for the current study in September of 1995. The applicant met with FDA on several occasions following initiation of the study to discuss issues of end point definition and analysis. The NDA itself was submitted in March 31st of 1997.

In a special considerations meeting with the FDA on September 15, 1997, the applicant requested that FDA consider a change in the indication to target third-line systemic therapy in patients previously treated with Doxil.

The applicant's pivotal study was conducted between September 1995 and March 1997 and enrolled 89 patients with advanced AIDS-Kaposi's sarcoma in nine centers located in California, Massachusetts, New York and Florida. Literature reports on three other studies were also included in the application, as shown on this slide here.

All studies are single arm, open label Phase II studies. The dose and schedule chosen for the pivotal study was based on Study No. 139-281, conducted at the USC Norris Cancer Center and at Massachusetts General Hospital, both participating centers in the current study. A Brown University study enrolled only four patients and used a markedly lower dose of paclitaxel and will not be considered further in this presentation. Both studies 139-174 and 139-281 have previously been presented to this Committee.

The only study, it should be pointed out, using the applicant's formulation is the pivotal study. The other studies used the currently approved formulation. It should also be noted that the formulation used in the applicant's clinical study is not the same as the formulation which is intended for marketing.

The study objectives were first to determine response rate and median time to tumor progression for patients with advanced refractory AIDS-related Kaposi's sarcoma treated with a three hour infusion of Paxene at a dose of 100 milligrams per meter squared every 14 days. Secondly, to determine the toxicity profile of this dose and

schedule. And thirdly, to evaluate clinical benefit in this patient population.

Quality of life in the pivotal study was also assessed using the Symptom Distress Scale. However, the applicant was advised that the FDA regards interpretation and reliability of quality of life data collected in single arm, open label studies as problematic.

As pointed out by the sponsor, eligible patients have had to have failed at least one prior systemic chemotherapy regimen. And acceptable indications for treatment included one or more of the following: multiple, more than 25 mucocutaneous lesions; visceral involvement -- initially symptomatic visceral involvement was required, however this was later changed to allow the simple fact of visceral involvement to qualify for entry; and finally symptomatic lymphedema.

Initially, at least five measurable cutaneous lesions were required. This was later changed to specify that these lesions must be raised. Response was graded using a modification of the ACTG criteria initially described by Crown, et al.

In this system, a complete response in accordance with standard oncologic practice requires

the complete disappearance of any detectable residual disease and this must persist for at least four weeks. Please also note that biopsy documentation of the absence of disease is required when flat lesions persist.

Partial response requires the absence of any new lesions or edema and also any one of the following occurrences: either a greater than 50 percent decrease in lesions counts that persist for at least four weeks; a greater than or equal to 50 percent decrease in the total area of the five marker lesions or complete flattening of at least 50 percent of all previously raised lesions. Note that according to the protocol, only the decrease in lesion count required 28 day confirmation.

Criteria for progressive disease require only the demonstration of new or progressing visceral disease, new or increasing tumor associated edema, a greater than 25 percent increase in the total lesion count, a greater than or equal to 25 percent increase in the total area of the marker lesions or a change in the character of at least 25 percent of all previously flat lesions to raised.

Please note that unlike progression criteria in other solid tumors in which a single new

lesion would indicate progression, in this system a 25 percent increase in the total lesion count is required.

I would like to point out two difficulties with the current definitions, while at the same time acknowledging that a joint effort of the AIDS Malignancy Consortium, the National Cancer Institute and the FDA is currently underway to revise these criteria.

First, the criteria did not explicitly resolve the situation in which a patient progresses on one of the three response subscales prior to responding on either the same or a different subscale. And second, the criteria did not clearly specify the method of calculating progression based on lesion flattening. It is important to emphasize the criterion in current use were applied to this application.

The protocol specified that overal response was to be limited to the first ten cycles. However, after inspecting the data, it became clear that late responses on one of the three subscales, tumor lesion count, tumor size and nodule flattening, occurred in at least eight patients and therefore, a response was credited regardless of the time in which

it would occur.

Although the protocol did not explicitly state this, confirmation at four weeks was required for all partial responses not only for responders on the total lesion counts. This is in accordance with standard oncologic practice and the applicant has accepted this modification in communications following distribution of the draft medical officer review.

Based on information previously supplied by other investigators in this field, patients who progress on any subscale were deemed progressors, regardless of subsequent responses.

A total of 89 patients were enrolled with a median Karnofsky performance status of 80 percent. In general, the study enrolled patients with advanced disease in that at least 80 percent of patients were poor risk on at least one of the prognostic staging subscales. In tabulating the indications for treatment, it can be seen that 80 percent of patients required treatment for multiple cutaneous lesions. A total of a third of the patients required treatment for visceral lesions either symptomatic or asymptomatic and approximately half had symptomatic lymphedema. Exactly half had symptomatic lymphedema.

The patient population also fit the

description of refractory disease. Although the median number of received prior chemotherapy regimens was one, there was a maximum of five, and there is a significant percentage of patients who have had at least two prior regimens. Between a third and a half of the patient population had received and failed prior therapy with either Doxil or DaunoXome or both and the majority of patients had stopped their last systemic chemotherapy regimen prior to entry on this study because of either inability to tolerate treatment or because of progressive disease.

At least a third of patients had progressed through their immediately preceding chemotherapy regimen.

For the Committee's reference, this analysis is labeled the Per Protocol Analysis in the draft medical officer review previously circulated. After extensive review and discussion of further additional data submitted by the applicant, the primary FDA analysis concludes that this study shows a 42 percent response rate using the previously cited interpretations of the protocol. All responses were partial and no complete responses were noted.

The median duration of response is 13 days, although this has not been confirmed by our

statistician. The time to response was 34 days and the median time to progression calculated using 37 events and 51 censored observations was 163 days.

In accordance with the applicant's request at the special considerations meeting, the issue of response in patients with prior Doxil therapy was examined. Twenty seven patients in this study have previously received Doxil. Thirteen as first-line treatment, and 14 as second-line or greater.

Amongst the 13 patients receiving Doxil as first-line treatment, there were three partial responders for a 23 percent response rate using the response categories assigned during the primary FDA analysis.

In the 14 patients receiving Doxil as second-line or greater treatment in which Paxene therefore would have constituted third-line or greater treatment, there were six responders for a 43 percent response rate.

This slide shows the areas of discrepancy between the applicant and FDA in accounting for the responses. Please note this compares the revised FDA primary analysis with the applicant's revised analysis which they have presented. Let me bring that up for you. The major problems can be seen to be -- to occur

in the patients with responders, claimed responders who progressed prior to the actual observation of a response. Please also note that there was one responder credited who could not be documented to have a greater than 50 percent decline on any of the response subscales. And please also note that the FDA review upgraded three patients from the stable disease category to the partial response category.

The overall response rate of all enrolled patients observed in the two major studies from the literature are shown here. Although it should be noted that data for these studies were not submitted to the FDA and only the published literature reports were included.

In Dr. Gill's study, which was again as noted the pilot for this study, there was a 59 percent overall response rate in all enrolled patients. In the 40 patients who had been previously treated, there was a 52 percent response rate.

While the publicly available results from these studies appear encouraging, the Agency regards them as sufficiently different from the pivotal study in both design and execution, that any formal, direct comparison would be inappropriate.

One issue that arose in discussions with

the applicant following the initial circulation of the draft medical officer review is the possibility of multiple valid interpretations of the progression criteria. Shown here is the clause in question. With the Committee's permission, I would like to take a few minutes to present a short example that illustrates the difficulty.

This is an example selected from the submitted database. The ellipses here indicate data that were excluded to ease a presentation which neither add nor detract from the point of this presentation. Shown here are the cycle number, the day of therapy, the observed number of flat lesions at each time point, the calculated number of flat lesions at each time point, the observed number of raised lesions at each time point, and the change in the number of raised lesions from the previous cycle. The line shown here in magenta represents the nadir of the raised lesion count.

Based on extensive correspondence with the applicant and the extensive and internal discussions, there appear to be at least five separate methods of determining progression. This becomes important because a patient's overall response integrates the outcomes on the three separate response subscales.

Thus, for instance, an initial early progression based on lesion flattening would result in a patient being considered a progressor despite the occupance of a later response on the basis of tumor size or total lesion count.

Now Method 1A would use as the method of determining the baseline for progression, the observed number of flat lesions at the nadir of raised lesion. In this patient, it would select a reference value of 30 and 25 percent of that number, or seven new lesions would be required for the patient to progress.

Method 1B, which is the method used by the applicant, models the number of flat lesions at the nadir of the raised lesion count. In this patient, it would select a reference value of 41 and then ten patients or ten lesions, excuse me, would be required for this patient to progress.

Method No. 2 would use the observed number of flat lesions in the cycle immediately prior to the nadir of the raised lesions as the baseline. In this patient, it would select a reference value of 17 and four lesions would be required for progression.

Method No. 3 uses the number of raised lesions that flatten by the nadir of the raised lesion count as the baseline against which progression is

judged. In this patient, it would return a value of 33 as the reference, and therefore, eight new lesions would be required for progression.

Method No. 4, which was the method adopted in the original FDA draft medical officer review, chooses the nadir of the raised lesion count as the reference value -- as the baseline. In this patient, it would select a reference value of five and therefore only one lesion would be required for the patient to progress.

Each of these methods, although there are multiple, has been applied by either the applicant or one of several FDA reviewers in an informal survey taken within our division. Again, emphasizing that Method 1B was applied to this application, Method No. 4, it should be pointed out, most closely corresponds to the response criteria being developed currently in the NCI/FDA/ANC collaboration.

To repeat the earlier slide showing the actual data, Method 1A would select a reference value of 30, Method 1B would select a reference value of 41, Method 2 would select a reference value of 17, Method 3 choosing the number of flat -- lesions that flattened would choose this number here, 33. Method 4 which is the number used in the original FDA review

would choose a number of 5. And again, Method 1B is the applicant's -- method applied by the applicant.

If one classifies this patient according to each of these different methods, one comes up with these outcomes. And the point here is the extreme variability in outcome resulting from these different methodologies. There is a ten fold variation in the number of lesions that would be required for progression, a nearly four fold variation in the day and the day on which progression occurs, and diametrically opposite response categorizations, depending for this response scale anyway, depending on the method chosen. In fact, according to Method 1B the patient would never have responded prior to the end of treatment and would have remained as a partial respondent throughout his entire course of treatment.

Presented here are the response rates from the original review, shown for comparison and labelled draft FDA analysis which again used Method 4 and showed a 35 percent response rate. And the revised FDA analysis which followed Method 1B, which more closely approximates the current practice. The estimate shown here, 42 percent, is our best estimate of the response rate from this study.

Also shown here for comparison are two

secondary analyses, and I apol ogize at this point for a typographical error in the handouts. The firs t analysis, which is labeled as the relaxed FD A analysis, was carried out to account for th e subjectivity which is inherent in the measurement and counting of Kaposi's sarcoma lesions and to al l account for the clinical observation that initiall y confluent lesions may occasionally breakup and mak e the tracking of any individual lesion difficult.

If you adjust for these factors o f observer variability, one comes up with a respons e rate of 45 percent. An analysis excluding fiv e patients who were ineligible for the study on th e grounds of significant medical reasons, yields a response rate of 42 percent, that is 34 responders ou t of 81 patients. Both calculations of this respons e rate are essentially identical to the 42 percen t obtained in the revised primar y analysis using Method 1B.

Moving on to the elements of clinica l benefit. Twenty five percent of 24 patients wit h disfiguring facial lesions who had assessabl e photographs submitted showed improvement in thei r disfiguring facial lesions. W hile nine percent of 11 patients with foot lesions who had assessabl e

photographs submitted showed evidence of improvement, and 12 percent of 48 patients who had lymphedema who had assessable photographic evidence submitted had improvement.

The submitted quality of life data is weakened by the fact that it was collected in a single arm, open label study and therefore lacks comparator to assess the extent or the impact of the extent and nature of the missing data. For similar reasons, which are outlined in more detail in the medical and statistical reviews, interpretations of analyses aggregating more than one subscale are also considered to be difficult.

Nevertheless, they made provide additional helpful information in interpreting the response and clinical benefit data presented. This slide depicts the result of a longitudinal data analysis performed by Dr. Koutsoukos, the statistical reviewer, on the mobility data using response assessments from the draft FDA analysis. He performed a similar analysis to this using the response assessments from the applicant's initially submitted analysis and obtained essentially the same results. Therefore, only this will be shown.

On this scale, a decrease in score

represents an increase in an improvement in mobility and time in cycles is indicated here on the X axis. As you can see, there is no statistically significant difference in the rate of improvement between non-responders which are indicated in the lower line and responders which are indicated by the top line, although there is an improvement from baseline. Thus, although an unadjusted analysis which pools all patients together, irregardless of response status does show a statistically significant overall improvement in mobility over time, this improvement cannot be ascribed to differences between responders and non-responders.

For the sake of completeness, statistically significant improvements over time were noted in the unadjusted analyses of Appearance No. 1 which measures the worsening of appearance, mobility as shown here, breathing and Karnofsky performance status. However, analyses such as the one indicated on this slide do not show any difference between responders and non-responders on any of the subscales.

This slide shows the response of patients with pulmonary involvement that had evaluable data. Although the bottom line of 60 percent does appear impressive, it should be noted that it is drawn in

five patients which represents a very small subset, 18 percent to be precise, of the 28 patients with visceral disease who were enrolled in this study.

I should also note that the responses in visceral disease all occurred in patients with pulmonary lesions. This slide again depicts the work of Dr. Koutsoukos on a performance status of data. It should again be noted that there is no difference between responders indicated here, and non-responders indicated here.

Although there is again a significant improvement over time from baseline, on this scale again an improvement, unlike the previous scale, is indicated by increase in the Y axis and again, time and cycles is indicated on the X axis. And again, the same comments made previously in reference to the mobility data also apply to this data.

Turning to the safety analysis, the applicant reported a total of 22 deaths, of which 11 occurred at greater than or equal to 30 days beyond the last dose of study drug, and seven which were possibly related to Paxene.

These seven deaths were distributed in the following manner: five of them -- five of the 22 were attributed to cytopenia complicated by infection; one

occurred as a result of a septic shock complicated by respiratory arrest; one occurred in a patient who had pulmonary hypertension with congestive heart failure for the total of seven deaths.

This slide considers the occurrence of opportunistic infections according to whether the event represented a new event, the continuation of an already established infection in that patient which became established prior to entry to study, or recurrence of a previous infection. There was one patient in which such classification could not be made.

Although definitive conclusions cannot be drawn from this study due to the lack of a randomized concurrent control arm, as a general statement, the instance of opportunistic infections does not appear unexpectedly high for this patient population and the profile does not show an unusual distribution of infectious organisms.

As expected, myelosuppression was substantial with more than 80 percent of patients having either neutropenia, leukopenia or anemia. Approximately a third of patients had thrombocytopenia and there were 11 patients or 12 percent in whom their neutropenia was complicated by febrile neutropenia

which was defined as fever occurring during a period in which the neutrophil count was less than 1,000 whether or not infection of a specific organism was documented.

The use of hematopoietic support was liberal with 41 percent of patients requiring the use of supplemental PCSF and 25 -- a quarter of patients requiring either erythropoietin or red cell transfusions.

This study included a substantial number of patients taking concomitant protease inhibitors, although again lack of a concurrently randomized control arm prohibits the drawing of definitive conclusions regarding the presence or absence of drug/drug interactions.

Known toxicities of protease inhibitors include hyperbilirubinemia, diarrhea and renal calculi and there were six patients shown here -- or nine patients in whom an isolated elevated hyperbilirubinemia was observed as their only instance of hepatic toxicity. In each of these patients the time course was consistent with the hypothesis that they represented the effect of protease inhibitors as opposed to Paxene toxicity.

Twenty nine patients, or 32 percent, had

arthralgia, myalgia, or severe arthritis which could not be easily ascribed to a specific etiology apart from the study drug and therefore the Agency adopted a conservative position and ascribed the toxicity to the study drug. There were ten patients in whom nephrotoxicity occurred. Approximately a third of the patients had neurotoxicity, 88 percent of patients had hepatotoxicity and there were three patients in which either frank malignancy or an unexplained generalized lymphadenopathy occurred.

In summary, the submitted Phase II study of Paxene in patients with previously treated Kaposi's sarcoma should be considered an adequate and well controlled study of objective tumor response. The objective response to Paxene in this patient population may be a clear demonstration of anti-tumor activity with the comparator in this case being the known natural history that the tumors do not shrink without treatment. And the overall objective tumor response rate was well documented at 42 percent of patients.

However, proof of clinical benefit is less clear with improvement in only 25 percent of patients with disfiguring facial lesions, nine percent of patients with foot lesions, 12 percent of patients who

had lymphedema and 60 percent of a very small subset of patients with lung involvement.

The study was not adequate nor well controlled to evaluate the secondary end points of time to progression, duration to response, or survival. Thank you.

CHAIRMAN DUTCHER: Questions from the Committee for the FDA? Dr. Simon?

DR. SIMON: Could you say anything about duration of response?

DR. KOBAYASHI: Yeah, the overall duration of response is 213 days. Although the reason it is not on the slide is we have not had time to have that confirmed by the statistician.

DR. SIMON: That's the median --

DR. KOBAYASHI: That's the median duration based on a Kaplan Meier analysis.

DR. SCHILSKY: Ken, I had just two questions. You mentioned right at the beginning that the formulation which is proposed for marketing is different from the formulation which was actually studied as under the Phase II study. Could you comment on that any further with respect to the FDA's level of comfort that the proposed formulation is actually equivalent to the formulation for which we

have seen data.

DR. KOBAYASHI: I think that involves some proprietary considerations. I think perhaps the company would be, or our chemist would be, perhaps, better suited to answer that question. Or perhaps one of my superiors.

DR. SCHILSKY: I just think it's going to be a little bit difficult for us to make a judgement about these data --

DR. KOBAYASHI: I understand.

DR. SCHILSKY: -- if what we have been spending the morning listening to is not even the drug that's being proposed for marketing.

DR. KOBAYASHI: I understand.

DR. DELAP: Well, I think we are basically satisfied that the data that you have seen a representative of the data that would be generated if the precise formulation to the market had been studied. And I don't know if the company wants to contribute anything about any differences that there might have been, but there are bridging data that enable us to feel pretty secure that what we are looking at is the reality.

DR. SCHILSKY: So if you are secure, then I'm satisfied. And I guess my other question comes

back to this issue of hepatotoxicity from protease s and I was just wondering if in your review of the dat a whether you were able to sort of get into enoug h detail to figure out if a patient had, say, a n elevated bilirubin attributable to protease inhibitor s and was receiving Paxene at that point in time, did i t appear that the patient had an y greater toxicity from that cycle of Paxene during which the bilirubin wa s elevated?

DR. KOBAYASHI: No, I did not. W e conducted analysis comparing the toxicity according t o whether or not the patients had received proteas e inhibitors or not and we broke that down, the hepatic component of that and tried to tease out whether this was isolated hyperbilirubinia due to proteas e inhibitors or whether or not, or we didn't look a t specifically the subset of patients who had elevated liver functions going into the study and whether o r not they had any different toxicity experience . That's certainly something tha t we will be looking at after this.

DR. NORTHFELT: I have another questio n related to protease inhibitor antiretroviral therapy. You mentioned in your closing statement that a goo d control for these data would be the experience that K S

does not regress unless it's treated, I presume you meant with chemotherapy.

Now, at the coffee break Dr. Aboulafia and I were telling each other our fish stories about regression of KS under the influence of potent antiretroviral therapy with no chemotherapy. We both had patients with pulmonary KS or lymphadenopathies KS which is resolved substantially or completely, in a clinical sense, with no chemotherapy.

So, could you just reflect on that a little bit for us? Because we've heard how we don't have very good control on antiretroviral use here.

DR. KOBAYASHI: I understand your point. The point being that there is a second potential medication being administered to these patients which could account for these responses. And how can we reliably attribute the observed responses to Paxene as opposed to say the administered protease inhibitors or whatever?

I think that's an excellent question and a very important issue. And it highlights the difficulty with interpreting, a couple difficulties actually. The first one is the simple off-the-cuff highlights difficulty with interpreting data from single arm, non-randomized Phase II study in which

there is not a concurrent control arm. It also highlights the difficulty that the pace of medical progress is rapidly changing and we are talking about great improvements in our other -- in treatment for AIDS.

And so, how to factor that into designing a study or looking forward to anticipating the next step in response to your question, how one would design that study given the realities of patient care in 1997 is a little bit more problematic and one in which I do not have a ready answer.

DR. MARCO: Well, first I want to make a comment that we just, we can't be saying protease inhibitor and thinking that they are all alike or that all regimens are alike. I mean, Donald, I'm sure you treat your patients very well and you know exactly what to give them and what combinations. But, listening to some of these patients speak and the therapies that they were given for their KS, I mean it just shows how patients are not always treated properly. It's sort of embarrassing.

What my question for you is, I'm having trouble with the numbers as far as patients that were evaluable, i.e., if they had more than two cycles of therapy versus the patients that you talked about

having protocol violations. You originally say that 14 out of 89, 16 percent were protocol violations. Nine out of 89, ten percent lacked positive histologic confirmation. How does that figure into your percentages in your final lab?

DR. KOBAYASHI: Right, after that draft went out, we had communication with the sponsor and they were able to supply us with biopsy reports for one thing, and were able to satisfy us in several of the patients which appeared to be ineligible on the basis of the data which was initially submitted did in fact have sufficient data to support eligibility for the trials. That is part of the discrepancy in the numbers.

DR. MARCO: Okay, so -- I'll let you finish. I'm sorry.

DR. KOBAYASHI: And the other response is that in discussing that slide I did think the disclaimer that five patients were exclusions on the basis of significant medical reasons. Considering the nature of this study, the physicians involved, and absolute lack of a biopsy report was not considered to be a significant medical reason, especially after we were able to get the documentation.

So these five patients that are excluded

here are patients who, for instance, one had a clearly elevated creatinine that should not have been elevated, or should not have entered on the study under the protocol criteria, that sort of thing.

DR. MARCO: Okay, so five you basically threw out.

DR. KOBAYASHI: Right.

CHAIRMAN DUTCHER: Dr. Temple?

DR. TEMPLE: Ken, as part of the response to Dr. Northfelt's question about the adequacy of the historical control that you have patients both on and not on protease inhibitors and look at response rates in both of them. Right?

DR. KOBAYASHI: I'm sorry, I was --

DR. TEMPLE: Isn't part of the answer to Dr. Northfelt's question about the adequacy of historical control always a very good question to ask in changing circumstances --

DR. KOBAYASHI: Yes.

DR. TEMPLE: -- that you have patients both on and off protease inhibitors. You are getting smaller sample sizes, of course, by that time, but the response rates are not very different in those two groups?

DR. NORTHFELT: Yes, my response to that

would be that there is protease inhibitors therapy and then there is protease inhibitor therapy. I mean there are people who have viral loads of a half a million on protease inhibitors and there are people who have viral loads of ten on protease inhibitors. And both of my colleagues here have pointed out that without a real understanding of how well the protease inhibitor therapy is working, you can't know how much it confounds the observations of the chemotherapy.

DR. SIMON: Yeah, but some of the patients are not getting any protease inhibitors and they are responding, so --

DR. TEMPLE: Yes, so it can't be all that they are on protease inhibitors.

DR. NORTHFELT: Agreed. But they may have good immune system response to their HIV that keeps their viral load as low as any protease inhibitor treated patient in the next chair. So, we just don't know enough about these patients I think.

DR. TEMPLE: Concurrent controls are better.

DR. BRODER: May I respond.

CHAIRMAN DUTCHER: Sure.

DR. BRODER: I thank the Chair's indulgence. We performed an examination of the

duration and the speed with which a response occurred. And there is a definite fund loading of response in patients. It does not occur by chance or randomly throughout the observation period. There is a slide which was shown that could be presented again.

So there is a highly statistically significant front loading of the responses juxtaposed to the administration of the Paxene. This makes it exceedingly improbable with P values that our statistician could give you, that this is just occurring on a spontaneous basis across the observation period. But there was a front loading of the response rates and I unfortunately can't show the slide, but we'd be happy to provide it to the Committee.

DR. ABOULAFIA: Could you go back one slide on your presentation? And could you just comment on this again, I'm not sure I understood your point here. It looks like you've taken into account disease, visceral involvement and a fair number or moderate number have responded. And I'm not sure I understood, Dr. Kobayashi, were you saying that a small number or a moderate number -- how did you put this data together in terms of a response?

DR. KOBAYASHI: This slide is just -- was

intended only to bring back from the previous slide, repeat information from a couple of previous slides all in one place so that the improvement on the four domains of clinical benefit for which we could have reliable information and could be put in one place.

There is no real point to this slide, it's simply -- or to this table -- it's simply there as a summary to aid and to deliberations we might want.

DR. MARCO: In relation to that, the -- I'm having trouble with the clinical benefit in completely understanding that the statistically significant betterment in appearance mobility and breathing, you agree with that, correct?

DR. KOBAYASHI: Yes.

DR. MARCO: But, that's under sort of the general well being versus these which are more specific to the lesions. How does this differ from what the applicant has shown us?

DR. KOBAYASHI: These were previously defined as the domains on which we would be assessing the response to the patient. One of the problems with looking at, with pooling different subscales from the quality of life data and perhaps our statistical reviewer could comment a little on this, is that there are a little bit -- there are a substantial number of

correlations between them. It's a little bit more difficult to interpret.

So we felt that, in terms of the quality of life data, that looking at a single response subscale would be better. As I say, in previous applications with AIDS-KS, we've sort of considered these domains to be the ones of the areas of clinical benefit. And I think Dr. Johnson had a comment he wanted to make.

DR. MARCO: Well, no, I just, but basically the sponsor showed us these beautiful graphs with these great P values and I mean either I'm getting it wrong or --

DR. JOHNSON: I think the, you are talking about two different things here. This is lesions that can be verified. In other words, we based our analysis here based on photographs of these lesions. I think it's fairly objective.

The quality of life data that the sponsor presented and that you are thinking about is the patients' analysis of whether the patient has improved. And we have some difficulties with that for methodological reasons that have previously been described. But the slides that the sponsor showed were based on the quality of life scales. These are

based on physical examination by the --

DR. MARCO: But you are considering physical examination, thus counting of lesions, clinical benefit.

DR. TEMPLE: No, these are individual patients who were thought to have had a persuasive improvement by photographs, sort of one by one. It's just different from an analysis scales or quality of life questionnaire.

It's not that they are inconsistent. They are just different ways of getting at the same kind of thing. And in this setting, there is a certain feeling that a response like that speaks for itself. If you have lesions all over your face and then they are gone, it's sort of obvious that was a benefit. And that's why these are -- there aren't that many of them, which is the point Ken made, but the ones that there are seem real.

DR. LI: I would add that this is perhaps the most conservative assessment because these are the ones where you can, as a dispassionate observer, Dr. Kobayashi was able to look at these pictures and say yes, you know, in this patient clearly the facial lesion got better. It's not to say that the lesions didn't get better in some of the patients, just that

he could look at photographs and say I wasn't there, I didn't see the patient, but just looking at these photographs I can verify that in this particular one. So I think these are kind of the most conservative view of data, but they are not inconsistent with the other views of the data.

DR. MARCO: I'm just having -- I understand that. I just having trouble with the semantics of it.

DR. KOBAYASHI: Oh, I'm sorry. I misunderstood the question.

CHAIRMAN DUTCHER: Any other questions, comments? Thank you. Okay, it's time to open the discussion. Are there any other comments? Should we go directly to the questions?

DR. NORTHFELT: Dr. Dutcher, could I just make a couple of comments? Thanks. I just wanted to make a couple of general comments about the nature of the research that goes on in bringing these drugs to review like this. I want to kvetch a little bit more about the response criteria, but I'll be very brief, I promise. And then I want to say something about natural history. I hope this will be of some value to the other members of the Committee. I think that's why David and I are here today.

First of all, the response criteria, I think Dr. Kobayashi did a very excellent job of showing how difficult it is to interpret the response data that are generated using these sets of response criteria. And, that is not the fault of the sponsor of the study. These response criteria have been foisted on them and on the KS-afflicted community by us in the clinical science community that can't do a better job of defining what constitutes a response to therapy in this disease. And there has been a struggle going on for ten years to try to create response criteria that actually expressed something meaningful about the way KS responds to treatment.

I think the clinical relevance of the response criterias that are in common use, the clinical relevance of those is very dubious. I don't think there is any reliable or reproducible relationship to anything clinically relevant using these response criteria. In other words, you can make the thing flat but not help a guy, or a thing can stay bumpy but he can still be helped by the treatment. And these response criteria do not express that.

Again, it is not the sponsor's fault. They were stuck with these things and they were struggling to the best of their ability, I think, to

show us that the drug does something. You know, but they are very handicapped by this monster that we have created in clinical science which is the response criteria.

Fortunately, thank God, there is a way out of this eventually and then this Committee won't be burdened with this problem anymore. There is this effort that was mentioned with the NCI and the FDA and the AIDS Malignancies Consortium to create some meaningful response criteria. I know there are people in this room who are developing other new drugs for KS that they hope to bring to this Committee's attention some day. So, please avail yourselves of the efforts that are being made by this Committee.

Dr. Murgo who is sitting here from the FDA who is very familiar with this is participating in creating these criteria. And I think it's going to be a major advance in our ability to really understand how KS therapy works. I just want to read very quickly from the abstract that describes this effort. This was presented at the AIDS Malignancies conference this spring. Dr. Feigel was the lead author and she said:

"Evaluation of clinical benefit is complex in

KS. The new criteria will focus on tumor specific symptoms, including evaluation both from the physician and patient perspectives. Categories considered significant include pain, edema, particularly extremities, scrotal and facial edema, facial and oral lesions, visceral-related symptoms and necrosis or ulceration of lesions."

So there you go, there is a nice list of actual, meaningful, clinical benefits that might derive from effective therapy.

And as soon as those criteria are developed fully and put into place, we won't have to go through this all and more importantly, Dr. Kobayashi, Dr. Murgo and his colleagues won't have to

go through the difficulty of trying to extract something meaningful from these data.

I also want to comment about something that appeared in the sponsor's information that we were provided. They tabulated response data from a number of studies of KS therapy going back over the years, and I think it should be brought to the Committee's attention that KS is different now than it was five years ago, or ten years ago. KS has changed profoundly over the course of the ten years that I've been caring for patients with this illness. We can use data on therapy for colon cancer from the 1980s. We can use data on chemotherapy for breast cancer from the 1980s to treat patients that we see today.

I don't believe that's possible with Kaposi's sarcoma. The natural history of the disease is changing before our eyes. The therapies for underlying HIV-related immune deficiency, as we have heard, are changing before our eyes. And so it's very difficult, I think, to look back more than a couple of years and really think that you are understanding what's going on with this disease.

I also wanted to point out, finally, that we heard comments from, I think, seven patients today who are on the study, and that's about ten percent of

the evaluable patients in the study, I think. So we had just before our eyes here, at least a ten percent response rate I think. And with that, I think a good case could be made that this is an approvable drug.

You know, there are a lot of caveats that we have been talking about all morning here, but we just heard from ten angels who are perched on our shoulders here this morning, telling us that something very healthful happened in their lives. And I think of everything that we've heard this morning, perhaps the sponsors should have highlighted their contribution to these patients. And I particularly want to thank them. I think they have brought something very meaningful to the eyes and ears of the panel.

CHAIRMAN DUTCHER: Thank you for your comments. All right. Should we go on to questions? All right.

This is question number one. "Is Paxene study size of 89 patients adequate for approval of a drugs for use after failure of a first-line or subsequent systemic chemotherapy for the treatment of advanced AIDS-related Kaposi's sarcoma?"

All those who feel that this is an adequate well controlled study and that the data

presented are sufficient for e valuation, please raise your hand. High.

One, two, three, four, five, six, seven, eight, nine, ten, eleven.

Question number two. If you l ook at your summaries that were in the blue folder, you hav e question number two has several tables in it tha t reiterate the data analysis.

DR. MARCO: Dr. Dutcher, can I make on e quick comment about question number one?

CHAIRMAN DUTCHER: Sure.

DR. MARCO: If I might. Granted th e applicant showed us that this is actually the largest patient pool for a study for second-line KS. An d that's great, but, and these studies are ver y difficult to do, especially because the instance of KS might go down. But I just wan t -- others in the room who are developing drugs who are hoping to get their drug approved for KS, whether it be used for KS o r possibly another cancer in the future, just being abl e to come to the FDA with such a small sample size t o get your drug approved on the fast track, i s problematic. So I think we need to start holdin g companies to a higher standard and for larger patient studies when they come to us in the future.

DR. SCHILSKY: I wonder if we could ask for clarification for our benefit from FDA, not so much about the sample size which I don't agree with anything you said, but about the study design. It was my recollection from one of the written documents that this submission is not able to be considered for accelerated approval.

If that's the case, I think we'd like to be clear on what the regulatory issues are. Because if it's not to be considered for accelerated approval, then does that put it -- do we need to be considering it with respect to whether there is appropriate comparator data, you know since we don't have a randomized trial. Maybe Bob you could clarify some of those issues.

DR. TEMPLE: Well, accelerated approval refers to willingness to approve a drug on the basis of a surrogate end point that has nothing overt to do with clinical benefit. It was not our view here that there was need for use of that consideration here because, as Ken showed you, there are at least 12 or 13 people who had persuasive clinical benefit, and you heard probably some of those people on that slide talking here today.

So, despite its name accelerated approval,

it's not an advantage to be under accelerated approval. It means you don't have actual clinical benefit demonstrated. The feeling here was that in this case there is.

The question is how much data you need and whether this is an adequate and well controlled study, albeit historically controlled study, is the sort of thing we invite you to discuss. Studies without control groups, without concurrent control groups are not our favorite kind of study because we like easy decisions. And every time you have a non-concurrently controlled study you have various agonies about how plausible the control is. And when the environment is changing, there are even more such agonies.

But, accelerated or not accelerated doesn't go to that question. The requirement for accelerated approval is adequate and well controlled studies that support the effect on the surrogate. And in this case, we are certainly mindful of the fact that we have information about paclitaxel and it's safety and things like that. So we are looking at a new use in a different population of a drug and the size of the database one expects there at least related to safety might be different from what you would expect if you were working up a drug de novo

that had never been in people before.

CHAIRMAN DUTCHER: Okay. Question number two. Paxene study resulted in a 42 percent objective response rate in 89 patients using protocol specified criteria. In an analysis using only eligible patients, the objective response rate was 46 percent. You may refer to the tables. The question being asked "Does the Paxene study show patient benefit based on the 42 percent cutaneous tumor response, the clinical benefit assessments and the quality of life assessments?"

Any discussion?

[No response.]

CHAIRMAN DUTCHER: Okay. All those who feel that the study does show patient benefit, please raise your hand. High. One, two, three, four, five, six, seven, eight, nine, ten, eleven. The vote is 11 yes.

Question number three. "Is the Paxene safety acceptable in view of the efficacy results and results available with alternative therapy?" All those who would say yes, please raise your hand.

DR. SWAIN: I'd just like to make one comment. I would definitely like to see more of the patitoxicity data looked at.

CHAIRMAN DUTCHER: Okay. With clarification of that patitoxicity particularly in the situation of protease inhibitors, is the Paxene safety acceptable in view of the efficacy results? Yes? One, two, three, four, five, six, seven, eight, nine, ten, eleven. The vote is eleven yes.

Question number four. "Is the Paxene NDA approvable for the indication of use after failure of first-line or subsequent systemic chemotherapy for the treatment of advanced AIDS-related Kaposi's sarcoma?" Dr. Ozols?

DR. OZOLS: Well here I think you have to address -- I mean, that's pretty broad. Three months ago we approved another drug. So how does that relate to Taxol? What about a patient who has received Taxol already for this indication, for basically the same indication that has progressed or stopped responding? Are we saying that they should also be candidates for Paxene?

CHAIRMAN DUTCHER: Dr. Johnson says no. Okay.

DR. JOHNSON: I think we thought that was obvious.

DR. OZOLS: Well, I mean are they the same drug, are they different drugs? Are you going to say

they are different formula drugs and there is different proprietary drugs, they may have different responses, toxicities? All that's been alluded to.

Are you saying that this is identical to Taxol?

DR. JOHNSON: We are not saying. That's yet to be determined.

DR. TEMPLE: That's not fundamentally different from what you make of the situation whenever there are two manufacturers who make the same active moidient to two different drug products. Usually you thought is if you failed on one thing, you wouldn't try the generic.

DR. OZOLS: Right.

DR. TEMPLE: If that were what the case was. But we have, I must say we have not actually told people that for reasons John just alluded to. We thought that was fairly clear. Different formulation, you know. One package in lipo somal, one not. that's a different question. But usually one thinks that they are pretty similar with respect to response rates. Of course, you have no data on that.

DR. OZOLS: Right.

CHAIRMAN DUTCHER: Any other comment?

[No response.]

CHAIRMAN DUTCHER: Okay. Is Paxene approvable for the indication of use after failure of first-line or subsequent systemic therapy for treatment of advanced AIDS-related Kaposi's sarcoma? All those who vote yes? One, two, three, four, five, six, seven, eight, nine, ten, eleven. The vote is eleven yes.

Any other comments?

[No response.]

CHAIRMAN DUTCHER: Thank you very much. The meeting is adjourned.

(Whereupon, the above matter was concluded at 12:22 p.m.)

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