FIFTY-THIRD MEETING

OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

CENTER FOR DRUG EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION

8:33 a.m.

Tuesday, June 24, 1997

Versailles I and II
Holiday Inn Hotel - Bethesda

8120 Wisconsin Avenue
Bethesda, Maryland

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ROBERT DeLAP, M.D.
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SUSAN HONIG, M.D. (A.M. Session)
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ON BEHALF OF JANSSEN RESEARCH FOUNDATION:

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APPEARANCES (Continued)

ALSO PRESENT:

RALPH BARCLAY
BETTY GALLO
JOANNE GOBER
HARRY B. HARRIS

C O N T E N T S

P R O C E E D I N G S

(8:33 a.m.)

DR. DUTCHER: Good morning. Could we have people please take their seats? We're going to begin.

Just to orient everyone, this is the Oncology Drugs Advisory Committee meeting, second day.

We're going to start this morning with a reading of the conflict of interest statement and then the open public hearing.

MS. O'NEILL-GONZALEZ: Good morning.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all 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), waivers have been granted to Dr. Sandra Swain and Dr. Richard Schilsky which permit them to participate fully in all matters concerning Janssen's Liazal.

In addition, general matters waivers have been granted to all committee participants who have financial interests in companies or organizations which could be affected by the draft guidelines to be discussed by the committee.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 of the Parklawn Building.

We would also like to note for the record that Dr. Robert Ozols and his employer, the Fox Chase Cancer Center, have interests in Pharmacia and Upjohn, the sponsor of a competing product to Janssen's Liazal, which do not constitute financial interests in the particular matter within the meaning of 18 U.S.C. 208. The agency has determined, notwithstanding these interests, that it is in the agency's best interest to have Dr. Ozols participate fully in all matters concerning Janssen's Liazal.

In the event that the discussions involve 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 may wish to comment upon.

Thank you very much.

DR. DUTCHER: In addition to the members of the committee, we'd like to welcome Mr. James Anderson who is our patient representative. Thank you for joining us this morning.

Now we're going to begin with the open public hearing. We have several people who have submitted statements and would like to provide a comment. The first person is Mr. Ralph Barclay. Please identify your affiliation and whether or not any financial support has been provided by the sponsor.

MR. BARCLAY: No, I don't have any affiliation except the support groups.

First of all, I'd like to say I was paid nothing to come here, and you may feel that that was an appropriate sum when I'm through.

(Laughter.)

MR. BARCLAY: In my written statement, I presented myself as a ME TOO advocate. I just want to say "me too" to the fine presenters that have preceded me and

are to follow me.

In other words, I would just like to sort of echo their thoughts and perhaps ask for the approval of Liazal, if it does seem promising. We understand your difficult position with everybody pulling on you like this with so many demands, but we prostate people would like your help and would greatly appreciate you keeping us in mind for developing new therapies.

Thank you.

DR. DUTCHER: Thank you very much.

Ms. Joanne Gober?

MS. GOBER: Good morning, ladies and gentlemen of the committee and audience. I come to you today as a surviving breast cancer patient of 10 years. My name is Joanne Gober and I'm from Charlestown, Rhode Island. My husband is a surviving prostate cancer patient of advanced prostate cancer of five years.

I have come today with a lot of difficulty financially because of our situation, and I did receive some assistance from Janssen, but it would not have prevented me from coming without the assistance. And I want to make that very clear.

My husband has been under treatment for the past five years with injections of Lupron and the following

hormonal blocking agents. He has been on Eulexin, Megace, Cytadren, Nizoral, nilutamide, and Liazal.

Through the willingness and only the willingness of our oncologist to constantly change these drugs and to work with us as patients to try to help him, we were able to lower the PSA every time it rose and put him out of remission.

Last August Frank's PSA escalated to 1,382, giving him extreme bone pain and total dysfunction. He was not able to walk and not able to even do normal things that most people are accustomed to. He required hospitalization and radiation in-patient and out-patient exceeding three weeks.

Through the assistance of a very dear friend, Lloyd Nade, with PACT, he suggested that I try to reach Janssen and see if I could get any information or find out about Liazal, which had shown good results. Only through diligence of working and asking and seeking help from lay people and people in the medical world was I able to get through to Dr. Kremer who, only through his compassion, provided the drug Liazal to our oncologist, and Frank started this drug last October 10th.

At that point, his PSA was 1,382. In December, his PSA dropped to 700. In February, it dropped to 683,

and his PSA this month, June 2nd of 1997, was 392.

He is a changed person. He is able to walk with a cane. He is able to go out and walk on the beach. He's able to drive his car. He's able to deal in a capacity that is normal or as normal as you can be with advanced cancer. This has only been accomplished with the aid of this medication, and this has only been accomplished because it has been made available to us, to our doctor and to us as patients, because somebody cared.

I think that's the message that everybody here has to hear is that somebody has to care. Certainly as people we know there are side effects to these drugs. We know that things could happen, but people, scientists, physicians, research people have taken as much time and as much effort to help people or to perfect these drugs so they can be safe. We're not safe from aspirin. When we take that, it has certain side effects.

But if Liazal is not made available, then there is no choice. I think this is the message that you have to hear. This is a miracle that my Frank has had because he was able to have this. Will he be here in six months? I don't know the answer to that, nor do I know the answer if he'll be here in a year. But I know he's here today. It gave us time that we would have not had.

I think the message that I need to tell you is that when you give your recommendations to the people in charge, the people that will make the decisions, not to think of how unsafe or is it proven, is it for everyone, but to think if this was my family, if this was my brother, my father, my grandfather, would I want them to have the opportunity to use this drug or not to use it.

This is all we can do as human beings. There is no guarantee, but the guarantee is that you did the best you could. You looked at a situation and you did the best you could to address it for everyone and let people make the choice. Let people with their doctor's guidance decide if this drug is good for them and will it help them.

It helped us. Frank would not be here today without it. We are totally convinced of this and not totally by things that are not proven. His medical history proves this.

Again, I thank you all very much for allowing me to come here today and to speak to you. I ask you in your hearts to look at this and look at it as something that can help people, that can help people who are afflicted with this horrible disease and give them a choice. When you give your vote or your recommendation, do it from your heart, not from a black and white scenario of

this is good, this is bad. Let people make that decision. If it means you gave someone 30 days or 6 months of life, then that's a good thing because it helped people be here that would not be here.

I thank you very much.

DR. DUTCHER: Thank you very much. Thank you for making the effort to come.

Our next speaker is Lieutenant Colonel Harry Harris.

MR. HARRIS: Thank you very much, madam. Good morning, panel members, ladies and gentlemen. I am Harry B. Harris, regular Army, retired Lieutenant Colonel and retired Department of State, Agency for International Development Foreign Service Officer.

I appreciate the opportunity to speak to you this morning. I am here as a Walter Reed Army Medical Center radical prostatectomy five-year survivor. I am also a member of several prostate cancer support groups in the area, to include the Walter Reed Army Medical Center's US TOO Incorporated, the American Foundation for Urologic Disease, Incorporated, the newly formed National Prostate Cancer Coalition, and the District of Columbia's Prostate Cancer Awareness Task Force Advisory Group.

You may ask why. I am in excellent condition,

but when I was on the bed recovering from radical prostatectomy, I promised God that if I were able to get up, I would go out and try to spread the word that prostate cancer can be conquered. So, after having heard Mrs. Joanne Gober, I am very happy to be here at this time.

My purpose for coming here is to request your approval for the immediate use of the Janssen Liazal, liarozole tablets. As you have heard, they may improve the quality of life for men suffering from excruciating pain due to advanced prostate cancer.

My symptoms of prostate cancer were detected early and I survived my April 1992 painless operation. I am advocating the use of an American drug discovered and being developed and may ease terrible pain for prostate cancer patients who may detect that disease after it may have metastasized.

I am not a lobbyist for any of the prostate cancer organizations cited above, Janssen, nor any other organization. I am here as a 76-year-old prostate cancer survivor to show you by my presence that the FDA's past approval of newly discovered and developed drugs helped save my life. Through your professional insight and to the economic, political, social, and clinical advantages associated with the use of new medical options for prostate

cancer patients, we would have more alternatives for our treatment. Your approval at this stage is requested and appreciated. Working together, we will accelerate America's pharmaceutical lead in prostate care.

God bless you, all prostate cancer patients and those involved in their care. Thank you very much.

DR. DUTCHER: Thank you very much.

Our next speaker is Mrs. Betty Gallo.

MS. GALLO: I say good morning to everyone, the committee and also the audience, and I want to thank you for allowing me to be here to testify.

I want to say that I received no assistance from Janssen except for my accommodations, but I would be here anyway in memory of my husband because I want to be able to save somebody else's life even though my husband is no longer with me.

I am Betty Gallo, the wife of the late Congressman Dean A. Gallo from the 11th District of New Jersey, who retired from Congress in August of 1994 and died from prostate cancer on November 6, 1994.

Unfortunately, when he was diagnosed in February of 1992, he was in the advanced stages of prostate cancer. How our life revolved around the PSA level and what future options were available for him.

I'm a prostate cancer advocate for the prevention of prostate cancer, education, awareness, and research. I'm here on behalf of Janssen and Liazal.

It is so important to have as many drugs available, especially in the advanced stages of prostate cancer. It can be given after a man is hormone refractory. The question is, what can I take after the hormone therapy fails? It gives the men and their families hope that if one drug doesn't work, that another one will. This is because in prostate cancer, there are so many variables. Each man responds differently to every medication.

I saw that with my husband Dean. When he was first diagnosed with prostate cancer in the advanced stages, he was treated at the National Institutes of Health in Bethesda, Maryland. With a PSA of 883 and a Gleason of 8, his life expectancy was three to six months, but because of the hope and new medications, he survived two and a half years.

Dean first started on suramin and combined hormonal therapy. His PSA level began to come down, but in October of 1993, it began to rise again. When it started to elevate, they gave him Cytadren. Dean's doctor, Dr. Meyers, told him a story about a gentleman who was on the same medication who had a PSA level of 4,000. He said this

man was basically put in a wheelchair and sent home to die. The man went home. The wife called up a couple weeks later and said there was medication called Cytadren and said would it be possible to give it to my husband, and Dr. Meyers, sure, there's nothing else I can do for him at this point.

So, they administered the drug and a couple weeks later she called back and he just assumed that she had called to say that he had passed away. She said, can my husband play limited tennis?

(Laughter.)

MS. GALLO: Unfortunately, Dean did not respond as well as this gentleman did. In January of 1994, they put Dean on tamoxifen, 48 pills a day. Can you imagine sitting there in Congress counting out 24 pills in the morning and 24 pills in the afternoon?

This unfortunately became toxic to his system. So, they had to wait because he had to have a hip replacement in March of 1994. They restarted him on 19 pills a day of tamoxifen when his PSA level at that point was 2,000. Within a month it did drop to 1,000.

Dean was then put on strontium 89 for bone pain.

All I can say is when my husband's -- after he

died, his medical records were this thick, but that's because of the hope that there were other medications available. If this prognosis had been the three to six months, his medical records would have been that thick.

Since his death, there are more breakthroughs such as this medication Liazal, and I'm sure that if there were more medications like Liazal available in 1994, my husband would probably have lived longer and made the quality of his life much better.

I just had a seminar in New Jersey put on by my task force of the American Cancer Society. I had a friend of my cousin's whose husband was just diagnosed about a month ago with prostate cancer in the lymph nodes. She and her husband came to the seminar and listened to the doctors talk about medications in advanced prostate cancer. It was the first time there was a hope for them than just the medication he was on, and if he does not respond to that medication, they know there is more available to them.

This year 30 to 40 percent of men over 50 will be diagnosed with prostate cancer.

One final thought. Do you or someone close to you have prostate cancer? Could you be next since one out of every eight men will be diagnosed this year with prostate cancer? Wouldn't you like to have that option

available to you, that there are drugs that you can use if one fails? How would you feel being incontinent or impotent, which is very devastating to men and their wives and their significant others? Don't you want the hope and options and a better quality of life?

The FDA should consider what will give men the hope and quality of life. I know Liazal will do this. You can never have enough medications available for prostate cancer. Every new breakthrough is one more piece of hope for a man and his family. Having that hope helps mentally to fight the disease. I urge the FDA to approve the drug Liazal to continue the hope that is so desperately needed.

Thank you.

DR. DUTCHER: Thank you very much. I'd like to thank all of the people who have come both yesterday and today to offer their thoughts. We realize they've made a tremendous effort to appear here.

Is there anyone else in the audience who would like to make a statement with respect to Liazal?

(No response.)

DR. DUTCHER: Just to let you know, this is the only time for open public hearing. If there are any members of the audience who would like to make a comment about the new initiatives that will be discussed this

afternoon, presenting an opinion or recommendation to FDA regarding these guidelines that are currently in draft form, this is the time to do it.

No? That being the case, then we will proceed with the morning's agenda and we'll begin with the sponsor's presentation regarding Liazal.

DR. BUSH: Good morning, everyone. I'm Dr. Janice Bush, Vice President of Regulatory Affairs at Janssen Research Foundation.

Today we will be discussing Liazal tablets for treatment of advanced prostate cancer. Dr. Alton Kremer, Group Director, Clinical Development, will present data on Liazal's safety and efficacy. Then Dr. Howard Scher of Memorial Sloan Kettering Cancer Center will discuss the value of post-therapy PSA decline in hormone-resistant prostate cancer. Then I'll return briefly at the end of the presentation to wrap up.

In addition, we have several consultants here to help us with questions later during the discussion period: Dr. Murray, Dr. Petrylak, Dr. Tsiatis, and Dr. Zeger.

As you've heard from patients yesterday and also this morning, metastatic prostate cancer is not curable with today's therapeutic options. Despite the

benefits of hormonal therapy, the median duration of progression-free survival of men with this disease is only 16 to 18 months. Virtually all will develop progressive disease after hormonal therapy. When this occurs, median survival is only about 9 to 12 months. Prostate cancer is now the second leading cause of cancer death in men, and in 1997 it's estimated that almost 42,000 men will die of hormone-refractory prostate cancer.

The treatment of relapsed metastatic prostate cancer has improved only marginally in the last few decades. Once hormone-refractory disease develops, there are very few therapeutic options available for these terminally ill patients.

So, there's a clear need for novel active agents. We are presenting the data on Liazal, an agent with a novel mechanism of action. It doesn't represent just another hormonal manipulation which has proven disappointing in the past. We will show that Liazal does work in the treatment of hormone-resistant prostate cancer and therefore offers these patients a new treatment option.

Janssen has submitted an NDA in support of the following: Liazal is indicated for the treatment of advanced prostate cancer in patients who relapsed after first-line hormonal therapy.

In support of this indication, we will show you that Liazal has produced longer survival in one comparator trial. PSA response is statistically correlated with survival and can be used to guide clinical use, and PSA-responding patients derive benefit that outweighs risk.

Now, Dr. Kremer will present the safety and efficacy data.

DR. KREMER: Thank you very much. I'm Dr. Alton Kremer. I'm an oncologist working with Janssen.

Hormone-refractory prostate cancer is a horrible disease and we do not treat it well today. As you've heard, with one in eight men eventually facing prostate cancer, this is a significant issue that we must address and it is in this setting I would like to discuss the efficacy and safety of liarozole.

This is a benzimidazole-derived agent, and it is the first of a novel class of differentiation agents that act by blockading retinoic acid metabolic pathway and therefore raising the intracellular levels of retinoic acid. This does not cause induction of retinoic acid metabolism, as can occur with exogenously administered retinoids. This agent has demonstrated antiproliferative effects in preclinical models of both androgen-dependent and independent prostate cancer lines and in breast cancer

cell lines.

The action of liarozole in blockading retinoic acid metabolism is shown here in a rat model. On the top slide, you see the increase in plasma retinoic acid with varying doses of liarozole, and more strikingly, on the bottom of the slide you see increases in the experimental tumor implanted in these rats consequent to the dosing of liarozole. There is a dose-dependent increase in the level of retinoic acid in these tumors.

It's also important to comment on what liarozole is not. This drug does not bind to the androgen receptor nor to the retinoic acid receptor, and it does not block adrenal androgen production.

When given chronically to humans, it does not suppress testosterone.

LNCaP cells, which are a prostate cancer cell line that in culture synthesize PSA -- when liarozole is added to these cultures, there is no artifactual suppression of PSA synthesis as can occur with some agents such as suramin.

This is not a direct cytotoxic agent.

The pharmacokinetics of liarozole have been well described. The drug is primarily N-glucuronidated. It is not itself a P450 metabolized agent.

The time to maximum level is approximately 30 minutes to 2 hours, and the half-life is approximately 8 hours.

There is no food effect, and there is excellent oral bioavailability.

In patients with prostate cancer, liarozole at a dose of 300 milligrams b.i.d., the labeled dose, has been tested in 383 such patients for over 150 patient-years of exposure. All doses of liarozole have been administered to 575 prostate cancer patients, for in excess of 200 patient-years of exposure.

We have conducted three key trials of liarozole in hormone-refractory prostate cancer. They're summarized on this slide.

USA-26 was a limited, 16-week randomized study looking at the effect of three doses of liarozole, 75, 150, and 300 milligrams b.i.d., and looking at the effect on PSA.

LIA-INT-5 was an open-label randomized comparative study looking at survival and comparing liarozole to cyproterone acetate, an antiandrogen that is licensed for use in many countries outside the United States.

LIA-USA-22 was similarly an open-label

randomized comparative survival trial comparing liarozole to prednisone 10 milligrams b.i.d. and was conducted in the United States.

The general scheme of these studies is outlined on this slide. All patients entering these trials had progressive metastatic prostate cancer following primary hormonal therapy. Their primary therapy could have been an orchiectomy or LHRH agonist with or without an antiandrogen.

Following progression, these patients were then randomized to one of the treatment arms in the three trials, and those are shown on the right-hand side of the slide with the patient numbers in each arm.

Please note at the time these trials were designed, the flutamide withdrawal or antiandrogen withdrawal syndrome had not been described and these trials did not take that into account. We have retrospectively examined the data in these trials with regard to antiandrogen withdrawal and I will present that.

I would like to summarize USA-26 briefly on this slide. As I mentioned, this was a limited 16-week trial looking at the PSA effect of 75, 150, and 300 milligrams b.i.d. of liarozole. The trial demonstrated a dose-dependent PSA response rate and a dose-dependent time

to PSA progression. Increases in liarozole dose correlated with decreased level of PSA.

Most importantly, when we looked at this trial retrospectively, the flutamide withdrawal effect did not account for the response rate of liarozole, nor did it account for the dose effect that was demonstrated in the study.

I'd like to move then to the two comparator trials I mentioned, one versus cyproterone acetate and the other versus prednisone.

In the final amended protocols and analysis plan, effectiveness was to be based on the following. The primary parameter for these studies was survival, and a difference was to be shown at p less .05. Please note that survival in these trials reflects all causes of mortality. It is not cancer-specific.

Additional parameters included response rate which could be used to demonstrate effectiveness if it was linked to clinical benefit for the patients.

Time to progression was also examined and this was analyzed on PSA, radiologic, and clinical progression events. The analysis plan called for a difference in time to progression to be shown if one such event was significant at p less than .05 and at least one additional

event showed a trend or better, p less than .1.

For effectiveness to be demonstrated on these additional parameters, the totality of the data was to be examined. Please note that the log-rank test was used for the primary analysis in the time-to-event variables.

The analysis plan specified the use of a Cox regression, and this was done to correct for baseline imbalances. At the time this analysis was planned and in fact I believe today, the literature is not clear on what the appropriate set of baseline parameters are for determining imbalance in prognostic factors. Therefore, we took a subset of the variables from the study for which there was literature evidence that they were potentially prognostic and by a stepwise algorithm narrowed that list to obtain the parameters for the Cox regression analysis.

Consequently the Cox regression analysis parameters were derived from the data and this analysis is considered a post hoc analysis. A validation package was suggested by the division for the post hoc Cox regression analysis and I will present those results.

The issue of tumor response in hormone-refractory prostate cancer is an important one. Measurable disease is uncommon in these patients, approximately 15 percent of any patient cohort.

Bone lesions are not useful for the determination of response. They are in general osteoblastic and exhibit a very prolonged healing time. Additionally, bone scan, as is usually the case, is not useful for the determination of response.

Today in the clinic, PSA changes are the method that is used by physicians in making treatment decisions for patients.

In light of this situation, there was an amendment to USA-22 based on an investigators' meeting in 1994 while the study was in progress. The original protocol used the National Prostate Cancer Program, NPCP, criteria for response and progression. These criteria were developed in the 1970s and for response rely on measurable disease and healing bone lesions and do not account for PSA, which of course was not developed until the end of the 1980s. In progression, these criteria do not define the symptoms, again of course do not account for PSA, and do not account for differing time-to-event progression parameters.

The amended protocol, therefore, defines response based on PSA and PSA response is to be correlated to clinical benefit for patients. Progression symptoms were defined as cancer-related pain, and as I mentioned

previously, the time to PSA, radiologic, and clinical progressions were evaluated separately.

I'll present the results from these comparator trials in this sequence, first looking at the log-rank analysis of survival, and then we'll talk about the baseline comparisons in these trials because hormone-refractory prostate cancer patients are a heterogeneous population of patients and it is well known that even small imbalances in important prognostic factors in heterogeneous populations can significantly influence the clinical outcome. Following that, I will present the survival analysis and then, importantly, the data on PSA response and its linkage to survival. Then I'll present progression and quality of life.

This is the log-rank Kaplan-Meier curves for LIA-INT-5, liarozole versus cyproterone acetate. You will notice there is not much separation of the curves, p .52, is not significantly different.

These are the survival curves for LIA-USA-22 by log-rank analysis. There is a separation of the curves but in fact it is prednisone that appears better, p .01.

I did mention, though, that we do need to look at the baseline comparisons and these are important in these trials.

This slide gives you a table of baseline comparisons in LIA-INT-5. All items are shown with an asterisk and those indicate parameters that had significant prognostic value from a univariate proportional hazards model. There is one univariate significant difference in pain and analgesic use. The others show some imbalances or trends, but again in heterogeneous populations, such imbalances may be important.

These are baseline parameters from LIA-USA-22 and here you see a much more significant difference at baseline. Again, start parameters had significant prognostic value in a univariate proportional hazards model. The ECOG score was highly significantly different at baseline in this trial between the two treatment arms, p .008. The other parameters in this table were significant as noted.

I note in this slide some additional baseline comparisons. These were not significant in a univariate proportional hazards model but do indicate some numerical imbalance and in all cases these are consistent with a poorer prognosis group assigned in the randomization to liarozole.

The Cox model was constructed as I described and the final parameters are shown here. They include ECOG

performance status, hemoglobin, alkaline phosphatase, PSA, and the duration of response to primary hormonal therapy in LIA-INT-5. This model was derived in the LIA-INT-5 data set and then shown to predict the behavior of the LIA-USA-22 data set. In the USA-22 study, because data was collected differently, time since primary hormonal therapy was substituted for the last parameter. All of the parameters included in the final Cox model have literature support as important prognostic variables.

This shows you the survival curves from LIA-INT-5 output from the Cox regression analysis. There is now a separation of the curves, and in fact liarozole is superior to cyproterone acetate, p .039.

On this graph, you see the survival curves from the Cox regression analysis for LIA-USA-22. The separation between the curves is now much narrower. There is still a trend in favor of prednisone, p .073.

Conclusions from the Cox model, therefore, differ from the unadjusted analysis that we conducted. Based on the Cox model, liarozole is superior to cyproterone acetate, and the differences from prednisone have become statistically insignificant.

In this setting, validation of the Cox model is extremely important. Two methods were suggested by the

division for this purpose. The robust inference method tests for the validity of a treatment effect in the event that the model is misspecified. The bootstrap analysis tests for the appropriateness of the parameters and of the model that is selected. In addition, we performed an outlier analysis because it is known that Cox models are sensitive to the presence of outliers.

On this slide you see the results of the validation package. On top in yellow I have put the original p values from the Cox regression analysis. On the left-hand side of the slide under LIA-INT-5, you see the results from each of the validation tests on the LIA-INT-5 study. There is a notable consistency to these data. In each case the result is the same. There's a significant difference between the treatment arms, with liarozole superior to cyproterone acetate.

On LIA-USA-22, there is a slightly different story. In this setting, the trend which you see in the Cox regression analysis does not appear robust and in fact there appears to be a sizable impact of outliers in this trial.

Consequently, to summarize the survival analysis -- and again, this is an analysis that includes all causes of death -- clinically important baseline

differences exist in these studies. The Cox model that was developed to account for baseline imbalance is robust and it is valid. After adjustment in the Cox model, liarozole is superior to cyproterone acetate and the differences from prednisone have become statistically insignificant.

In this setting, now I would like to turn to the issue of PSA response and particularly the linkage of PSA response to survival for these patients.

There has been substantial literature over the past several years linking PSA to clinical outcome in hormone-refractory prostate cancer, and Dr. Scher will address this in more detail later. For the purpose of these studies, PSA response was defined in the same way. A complete response, i.e., a drop to less than or equal to 4 nanogram per ml, or partial response, a decrease to less than 50 percent of the baseline level, had to be confirmed by a second determination at least 28 days later.

Progressive disease was determined as a 50 percent or greater increase over the lowest prior moving average of 3 consecutive points, and that was chosen to minimize artifact due to any laboratory variation.

Evaluable patients were required to have a PSA level of at least 20 nanograms per ml, and this helps exclude the possibility of de-differentiated tumors.

The PSA response rates in this trial are shown here. You'll note that there is a highly significant difference in LIA-INT-5 with a superior PSA response rate in the liarozole arm, 20 percent to 5 percent.

In USA-22, there is not a significant difference between the groups, 18 percent response on liarozole, 25 percent response on prednisone. That's not significantly different. Please note that in fact the pattern of response correlates with the outcome of the Cox model.

This slide shows you the accrual of PSA responders to liarozole over time, and you will note that responders are detected rapidly. By 8 to 12 weeks, approximately 90 percent of all patients who will potentially respond can be detected as having done so.

I mentioned before the issue of antiandrogen withdrawal. We retrospectively examined the data from these studies to look for the influence of antiandrogen withdrawal, and on the left of this slide, you see patients who had no exposure to an antiandrogen within 30 days prior to entering the study. The right are all patients. There are numerical differences that you can see in the response rates, but it is clear from this slide that PSA responses to these agents are observed in the absence of antiandrogen

withdrawal and in general the patterns are the same.

Now, if all we had was PSA response, we're just changing laboratory numbers on a slip, and that's not valuable. But the point is the linkage of PSA response to clinical outcome, specifically survival.

This graph shows you a landmark analysis at week 8 for LIA-INT-5, and you can see there is a difference that is statistically significant, p .032, between the PSA responders and the PSA nonresponders. PSA responders live longer by approximately 10 months, and this is in a landmark analysis that accounts for the potential of lead time bias.

The same landmark analysis at week 8 is shown here for USA-22 for both treatment groups. Again, there is a significant difference, p .005, between the PSA responders and the nonresponders. The PSA responders live longer by approximately 10 months.

You can see in your package on pages 111 and 114 curves that break out these landmark analyses by each treatment group and you see that the patterns are the same.

We also conducted a time-dependent covariate analysis to exclude the possibility that this is just a fortunate landmark. Again, for both LIA-INT-5 and LIA-USA-22, you can see that there is a significant difference

between the survival of PSA responders and PSA nonresponders.

This analysis was also stratified for baseline risk group to account for baseline prognosis, and the stratification breakout is in your briefing package on page 115.

Therefore, there is a strong and statistically significant correlation between PSA response and survival. This correlation cannot be attributed to baseline prognostic factors, as the stratified analyses continue to show the difference, and it is not sensitive to the landmark that is chosen.

In this table you see the times to progression in these trials shown in months. In each study you observe that there is one time-to-event parameter that shows a significant difference, p less than .05. In LIA-INT-5, liarozole has a significantly longer time to PSA progression, and in LIA-USA-22, prednisone shows a significantly longer time to subjective clinical progression.

However, there is no second time-to-event parameter that shows a trend, p less than .1.

We also examined the bone scan data in LIA-USA-22, as well as the soft tissue radiology, which I showed in

the previous slide. Again, looking at changes in discrete number of bone lesions or in the skeletal involvement index, there is no significant difference between liarozole and prednisone.

One exploratory analysis that we did conduct which is of interest is shown here and this comes from the bone scan data. You can see here that the number of discrete bone lesions in PSA responders increases more slowly over time than in the PSA nonresponders, and this is what one would expect based on the survival linkage with PSA.

In summary on time to progression then, for both LIA-INT-5 and LIA-USA-22, one time-to-progression event was significant, p less than .05, but no second event showed a trend, and consequently no treatment arm is superior in time to overall progression.

We did conduct Cox regression analyses for each of these time-to-event parameters, and at the suggestion of the division, we conducted a competing risk analysis for these parameters. The results are consistent.

Quality of life in these studies was measured by the FLIC scale, by ECOG performance status, and by pain and analgesia use scale, and in the United States as well by the MPAC scale. We conducted both the per-protocol

analyses, and also at the suggestion of the division, we conducted longitudinal analyses of the quality of life parameters. I'm going to summarize the longitudinal analyses results on the next slide.

In LIA-INT-5, liarozole showed a significantly better pain profile than cyproterone acetate. In LIA-USA-22, the liarozole group began with significantly worse quality of life scores than the prednisone group and ended with significantly worse quality of life scores. PSA responders also began and ended with significantly better quality of life scores than PSA nonresponders.

It should be noted that these longitudinal analyses are quite sensitive to attrition patterns and to missing data patterns, and therefore quality of life results should be interpreted cautiously.

I'd like now to discuss the safety profile of this drug both from the perspective of all prostate cancer patients treated at 300 milligrams b.i.d. and the two comparator trials.

This bar chart shows you the most frequent adverse events recorded for patients treated with 300 milligrams b.i.d. of liarozole in prostate cancer studies. The most frequent adverse events tend to be skin and gastrointestinal. This is fairly typical for a

hypervitaminosis A type pattern. In general, most of these adverse events were rated as mild to moderate. In each case less than 5 percent of the population reported the adverse event as severe.

Please also note that an individual patient can have more than one of these adverse events so that we cannot simply add one bar to the other to produce the sum of the two adverse events. It's not a unitary situation.

We examined adverse event discontinuations in these trials. These are patients that were listed by the investigator as having been discontinued for an adverse event. There is a difference between the numbers in this table and the numbers on your question handout, and that arises from the fact that we have excluded patients removed from the trial for disease progression in the international study. In this table you do see a higher rate of adverse event discontinuation in the liarozole group.

We examined the specific body system causes of adverse event discontinuations. Again, these are as recorded by the investigators. You can see on this table, particularly the top two lines, the biggest excess in causes of discontinuation are in the skin side effects and in the gastrointestinal side effects. When we looked at these skin side effects and the gastrointestinal side

effects, that were noted as causing discontinuation, more than 50 percent of the skin and more than 60 percent of the gastrointestinal events so noted were also rated as mild to moderate. These are the kinds of adverse events that can be managed with skin care and certainly with antiemetics.

We examined fluid and electrolyte balance adverse events in these trials, and you see in the liarozole column all 383 patients treated in prostate cancer trials and, for comparison, the two comparator arms in the two comparator trials.

You'll note on the top four lines that the overall signs of fluid overload appear similar across these treatment arms.

There is an increased incidence of CHF recorded in the liarozole patients in these studies, 7 percent to 3 percent and 3 percent respectively. We did look at the patients who were noted as having CHF and there is a statistically significant linkage to anemia at baseline. These patients on average had a further loss of about 1 gram of hemoglobin per deciliter from baseline to the time at which they were noted as having CHF. And there was also a statistical linkage to poorer ECOG performance status.

We also looked at outcome in these patients. In the two comparator trials, when one examines patients

with CHF who died in the presence of CHF, we see 4 percent on the liarozole arm, 2 and a half percent on the cyproterone acetate, and 1 percent on the prednisone. So, there is still a bit of an increase. We do not know if this is due to a sicker population or if it could be related to drug. It does, therefore, seem prudent that there be appropriate labeling in this regard and that physicians be cautioned to look for signs of CHF in these patients.

We did also note an increase in hypokalemia in the liarozole patients relative to the two other treatment groups, and again we're looking at all 383 liarozole patients but it's similar in the two comparator studies.

We considered the possibility that there was a mineralocorticoid mechanism based on deoxycorticosterone, but on the limited data that are available of paired data points, we don't see a correlation.

Hypokalemia is reported with other azole compounds and the mechanism for that is not known, but this is a side effect that is eminently treatable as well as preventable.

Therefore, in summary on adverse events, the most frequently occurring adverse events to liarozole are gastrointestinal or skin in nature and they are consistent

with its mechanism of action. These are largely mild to moderate in severity and they are manageable.

The excess discontinuations due to adverse events as well are primarily attributable to the GI and the skin adverse events.

The safety profile of this drug, therefore, is acceptable in patients with relapsed cancer with monitoring for signs of CHF.

To conclude on efficacy then, liarozole produces longer survival when baseline imbalance is accounted for than the comparator in one trial. That's the cyproterone acetate. The second trial did not show such a superiority.

PSA response, however, is statistically correlated to survival and it can be used to guide clinical use of the drug.

PSA responding patients derive a significant benefit from treatment. They have an increased survival of 9 to 10 months, and based on bone scan, they have slower progression of bony disease and they do have better quality of life scores.

PSA monitoring detects those patients who will benefit from drug and it does so after relatively short exposure, 8 to 12 weeks.

Most adverse events are acceptable and manageable.

Finally, in hormone-refractory prostate cancer today, the treatment options are limited and currently survival is short. Liarozole offers a new oral therapeutic option for patients who have very few options today. Patients who demonstrate a PSA response derive benefit from drug therapy that outweighs the risk.

I thank you very much and I would like to turn the podium over to Dr. Howard Scher.

DR. SCHER: Thank you very much.

Classical clinical trials in oncology rely on the entry of patients who present with bidimensionally measurable tumor masses that can easily be assessed post treatment. Such a situation rarely exists in prostate cancer as less than 10 percent of patients present with measurable tumor masses.

Furthermore, in most cases these represent lymph nodal metastases where the response does not parallel the changes that occur in bone, the most frequent and most devastating site of spread. It is clear, with currently available techniques such as bone scan in relapsed disease, that monitoring the disease in a serial way is extremely difficult and very hard to quantify in a reproducible way.

For individual patients, a PSA change would reflect changes in total tumor burden.

There are ample data to support a rising PSA after hormonal therapy bodes for a poor prognosis. Two large randomized clinical trials evaluating patients treated with combined androgen blockade, EORTC 30853 and SWOG INT-1, which included over 900 patients, clearly showed a sequence whereby if a PSA rise was documented post therapy, radiographic progression followed in a median of 5 to 6 months, and clinical progression, namely, an increase in symptoms occurred in a median of 4 months.

Thus, we opted to offer changes in therapy based on this initial PSA rise after hormones. PSA has the advantage over other techniques in that it is easy to monitor on a serial basis and in a patient who has shown progression prior to treatment, it would allow us to monitor and test new agents in a rapid way.

There are obviously pitfalls to using such a technique. Not all cells within a tumor express PSA, and it is clearly known that the PSA gene and PSA protein are subject to hormonal regulation. It is also clear from cell culture data that a PSA decline can be documented independent of killing cells. Such has been shown for suramin. Thus, we postulated that the validity of a post-

therapy PSA decline in clinical trials may vary as a function of the agent that is being tested.

The following slides illustrate some of the pitfalls and how we developed the two components of the criteria, namely, multiple determinations of a proposed outcome over time.

Here is a patient treated with a chemotherapeutic agent trimetrexate showing transient declines that coincided with the day 1 to 5 administration of the drug. You will notice, however, that over time these levels are serially increasing, and as such we would consider such a patient to be showing progression. Thus, in developing outcome criteria, the two critical components we required were that the given degree of decline be documented on multiple occasions and that it include some time factor.

Our first analysis consisted of patients enrolled in clinical trials treated at Memorial Sloan Kettering Cancer Center. It included a variety of therapies, all of which were nonhormonal. We used univariate techniques to explore the outcomes of patients utilizing prognostic factors that had been published as well as several new ones. We used the method of life table analysis, proportional hazards, and recognizing the

pitfalls in trying to compare responders versus nonresponders, we used the landmark method as originally proposed by Anderson and coworkers in 1983.

Furthermore, because we were using a single institution, nonrandomized data set, we thought it was important to obtain an independent data set of patients treated outside of Memorial, and for this we relied on our colleague, Dr. Sophie Fossa who had treated a cohort of patients in Norway.

In an analysis of 22 factors and multivariate techniques whether or not the patient achieved a post-therapy decline of 50 percent or greater was the most significant factor associated with survival.

This slide illustrates the comparative survival distributions of the Memorial Sloan Kettering Cancer Center and Norwegian treated patients. As you can see, these two populations are comparable.

The next slide illustrates the survival distributions of patients who achieved a post-therapy decline of 50 percent or more versus those patients who did not achieve a decline using the 8-week landmark. This landmark time was chosen because this is the most common time that we typically assess whether or not a given treatment is efficacious for patients undergoing therapy.

Our next analysis was recently completed and included a cohort of 254 consecutively treated patients on sequential clinical trials at Memorial Sloan Kettering Cancer Center. We again looked at the association of different baseline variables and outcome, and we also explored different rules or decision trees for PSA decline. Specifically we looked at whether two values were as informative as three values, whether biweekly determinations or monthly determinations were adequate, and we also explored different landmark periods, namely, 2 or 3 months based on practice patterns in different parts of the world.

We again went through a similar analysis with univariate techniques and developed a multivariate prognostic model.

For our validation data set, we combined the individual patient data, including 541 patients who were enrolled on INT-5 and USA-22, the trial just presented by Dr. Kremer.

Here is the summary of the data sets. 254 patients treated at Memorial Sloan Kettering, of whom 200 have succumb to disease. Janssen patients, 541, approximately 80 percent who have succumb to disease, reflecting mature data sets.

As you can see, the survival distributions are similar between the two groups, and the proportion of patients who reach the 60 and 90-day landmarks are included.

More importantly, in comparison to our previous analysis, a larger number of patients had achieved the outcome of interest, namely, a 50 percent decline in PSA from baseline so that we had more events to analyze using statistical modeling.

Once again, in univariate and multivariate analyses, the most significant factor was whether or not a patient achieved a 50 percent decline from baseline. We saw no difference in outcome whether the analysis included two or three variables or whether the 60- or 90-day landmark was used. This graph illustrates the comparative survival distributions of patients who achieved the 50 percent decline versus those who do not, essentially identical to our previous analysis, showing a marked difference in outcome.

For our validation set, we took the Cox scores of each patient and divided them into three equal groups, low, intermediate, and high risk. The comparative survival distributions are listed on this slide based on the observed and expected outcomes as the Janssen treated

patients were evaluated using the model derived on the Memorial Sloan Kettering Cancer data set.

As you can see, there is no difference on the 1, 2, or 3-year survival. This is illustrated graphically here, the observed and expected outcomes for the good, intermediate, and poor risk populations.

We next evaluated the question of whether or not PSA could serve as a surrogate marker for survival, and for this we used the Prentice conditions as proposed in 1989.

The first question using these definitions is whether or not the surrogate marker is affected by treatment. As illustrated here, the relative probability of achieving a 50 percent decline or not is significantly inferior for the patients who were treated with cyproterone acetate.

We next asked the question of whether the surrogate marker is prognostic. Shown here is the relative risk for patients who did not achieve a 50 percent decline using a 12-week landmark. As you can see, the relative risk of death is significantly higher for those patients who did not achieve the 50 percent outcome measure. I could add that there was an identical outcome whether an 8-week or 12-week landmark was used.

We next looked at the question of whether the effect of the surrogate marker was independent of treatment, and when treatments were added back into the model, whether or not the patient achieved the 50 percent decline remained the most significant factor. As you can see, for patients who did not achieve the decline within 12 weeks, relative risk of death remains high, exceeding unity, and this was not affected in this analysis by treatment.

Our conclusions from these analyses is that a post-therapy PSA decline is a prognostic marker for survival and the post-therapy PSA decline fulfills the conditions of surrogacy that were examined. These data show that PSA declines can be used as an endpoint for clinical trials, and for patients with prostate cancer, a post-therapy PSA decline is not only an index of efficacy but ultimately translates into a clinically meaningful outcome, specifically in improvement in survival.

Thank you very much.

DR. BUSH: Thank you, Dr. Scher.

Before we begin to answer any questions you might have, we'd like to suggest that during the committee's deliberation there be considered a fourth question. Now, we've talked to the division about this

earlier, so this isn't just coming out of the blue. We think this question could follow question 3, which I put up here for review purposes. That question is should Liazal be approved for the treatment of patients with advanced prostate cancer who relapse after hormonal therapy.

We would suggest that if the answer to number 3 is no, that the committee consider whether there's a subpopulation that can be identified for whom the risk-benefit ratio is acceptable and therefore warrants approval. You might guess from our presentation that we would have the suggestion that maybe PSA-responsive patients might be something to consider, but certainly the committee may have other thoughts and we would certainly welcome that dialogue.

I would also say too it might sound kind of strange for a company to, before we even hear what you have to say, suggest a more restricted label. I think that's because we really do believe this drug works and we want there to be options out there, more than what's currently there. So, that's the reason we're doing this.

Now we're ready to answer any questions.

DR. DUTCHER: Thank you.

Questions for the sponsor from members of the committee? Can Ms. Beaman ask a question first?

MS. BEAMAN: I'd like to see some more information please on the quality of life data that you may have accumulated.

DR. KREMER: Sure. I'd be glad to. Are there specific indices or anything in general?

MS. BEAMAN: The profile that was mentioned with CPA.

DR. KREMER: Okay. If I can have please our QOL slides, and what I would like is number 32.

This shows you two rather close lines, but these are the longitudinal profiles for the FLIC pain scale.

DR. DUTCHER: Can you raise the slides?

DR. KREMER: Oh, I'm sorry.

This shows you the longitudinal profiles from LIA-INT-5 for the FLIC pain scale for cyproterone acetate and for liarozole. I'm sorry. It seems to be floating a bit.

(Laughter.)

DR. GELBER: Can I ask you to show us the number of subjects that were evaluated over time when you show us this? You mentioned that there was a lot of missing data.

DR. KREMER: Missing data refers to dropout

patterns. So, this is essentially an intent-to-treat.

Dr. Rothman, can you comment please for Dr. Gelber in terms of number of patients?

DR. ROTHMAN: This is basically a projection over time. This is the random coefficient model. So, we start with the baseline values. We included everyone in there and it's a projection over the rest of the study. So, it includes all patients.

DR. JOHNSON: I'm sorry. You're going to have to explain how you project quality of life to me. I thought that was something that the patient assessed.

DR. ROTHMAN: Yes. What we did was we collected data -- and we had very complete data -- as long as the patient remained in the study. When they dropped out of the study, what this model does is project their trajectory over time. But perhaps Dr. Zeger could comment on the methodology.

DR. ZEGER: Actually to get back to Dr. Gelber's question, there was very substantial dropout as people were having events through the study. I think it was as high as 50 percent by the second month. So, there's very substantial dropout.

The methods attempt to make unbiased estimates of the difference between the two curves. There's not

filling in of data. People are only supplying data so long as they're in the study. There's no filling in, but what it's doing is so long as the dropout pattern -- the reason for dropping out depends upon things that we've already measured, for example, their previous quality of life scores or which treatment group they're in. The methods that are used will give valid inferences.

If the reason for dropping out depends upon things which we are not measuring -- and it's very difficult to know from a study like this whether that's the case or not -- then these estimates really will not be unbiased.

So, I think the qualitative message I would give to the committee is that with such a very large fraction of people dropping out, we've done the best that can be done with current methods, but there's no way to rule out the possibility that there are factors which are causing people to drop out and also affecting the quality of life score which we have not measured in this study.

DR. KREMER: I would note, just to follow your question with regard again to quality of life for PSA responders and nonresponders, I mentioned in the slide that scores were better in the PSA responders. If I can have slides 23 and 24 from this carrousel, I think again I can

show this point graphically.

DR. JOHNSON: Let me interrupt you to make a point and that is that you're focusing on the responders, but all the patients that entered into this trial received your drug that were on that arm. So, we really are not interested solely in the quality of life of the responders.

One of the other elements that we're interested in is knowing what happens to the patients who received the drug and do not respond. That's actually the majority of the patients. And we need to know that information as well.

DR. KREMER: Okay. Can we switch then for Dr. Johnson's question, if I may? If I can have on the GENBU carrousel, please, slide 36 which I think will illustrate the overall FLIC scores in the liarozole and the prednisone trial. We'll show you both the difference at baseline as well as the difference that persists through the study.

As you can see, there is a wide separation at baseline and there remains a wide separation throughout the study in this case. Prednisone patients begin and end with better QOL scores.

The slide that I put up initially from the LIA-INT-5 study is the same nature slide for liarozole and cyproterone acetate. It shows liarozole patients beginning

with a slightly worse score and marginally improving versus the cyproterone acetate patients, and in fact that was statistically significant.

So, those two slides do include all patients from both arms, and the point that I had wanted to make regarding the PSA responders is simply that that is consistent with the other pieces of the data.

DR. JOHNSON: Let me see if I understand this slide correctly. At about 6 weeks, it looks like there's an even wider splay between these two curves, for which we have no statistical analysis. I'm just looking at the curves.

DR. KREMER: Dr. Rothman, if you could comment please.

DR. ROTHMAN: One of the things that makes this a difficult analysis to interpret is that a large number of people dropped out between week 2 and week 4 in the liarozole group. What we do know about both groups is that those people with much lower quality of life scores dropped out, so this is biasing it downward at that point.

DR. JOHNSON: No. Actually that biases it upwards for the liarozole. If your worst quality of life patients fall out and your curve gets worse --

DR. ZEGER: No. Actually let me try to make

some correction about the method used.

The method used will not be biased by the fact that worse patients are dropping out. It's correcting for that effect. It's attempting to estimate what's the average quality of life for all people had they continued forward. The way it does that is by looking at what their trend was prior to dropping out and basically imputing the values had they continued. It's not treating those imputed data as if they're real data. It's acknowledging that that data is imputed and making estimates of confidence intervals that take account of the fact that imputation is being done. But the methods used will not be biased by the fact that people who are poorer previously are the ones who tend to be dropping out. It will not give a biased upward indication.

But I think her point is correct, that given there are so many people dropping out and given there's an imbalance in the rate of dropping out, I think you have to be cautious in interpreting this information.

DR. GELBER: That's correct. This is not the usual curves that we're used to seeing where the individual patient data are plotted, which is subject to that. This is a modeling.

But just one question on that. What kind of

assumption is made then in this modeling, if you can just describe that quickly to the committee.

DR. ZEGER: Yes, and maybe I could just add to Dr. Gelber's comment as well.

If we had just taken the mean value, mean quality of life value, for all the people who were still in the study, then if the people with poorer quality of life were dropping out, you'd see these curves starting to rise again not because they were getting better. It's just that there's a selection bias going on. But we did not use that method.

What we did is we used a method that basically estimates a linear or a quadratic curve for each person and then averages the curves. So, even if you give us a little bit of data at the beginning, if you're on a downward trajectory, we'll be averaging that downward trajectory at all the times and we won't get a biased inference. So, this is basically a random effects model with either a linear or quadratic pattern for each person and allowing for a different shape of the curve for the two treatment groups which is being shown here.

DR. JOHNSON: So, there is a break at 6 weeks that shows an even further downward trajectory for the Liazal.

DR. ZEGER: Perhaps we should get the specific p value for the curvature in that particular picture. I'll get back to you with that.

DR. DUTCHER: Dr. Gnecco, do you want to make a comment?

DR. GNECCO: I'd just like to bring up the point that in a situation like this, the approach that we take is that we look at completers and noncompleters individually. That's very important and we define completers after consulting with the clinicians and deciding what a clinician would consider an adequate course of therapy. Then you do this type of modeling to see if the patterns are the same for completers versus noncompleters, and if they are not, then you cannot use the data in aggregate like this. You have to look at those two what we call homogeneity groups based on this pattern of completing and not completing.

DR. JOHNSON: I actually have several questions, and I'm going to preface my comments by the following. This is not a process that takes place without input from the FDA from the standpoint how the regulatory process takes place. There's a lot of give and take between the sponsor and the FDA and a lot of advice that's given regarding the design and development of studies that

can lead to appropriate approval of products.

I think it's very important to point out that the sponsor was given some defined endpoints that they were asked to meet, and those are outlined in the sponsor's presentation. Specifically, they were asked to look for a survival advantage. They were asked to look for one of three measures of time to progression demonstrating a benefit for their product and demonstration of clinical benefit.

I want to address some very specific points that may seem a bit tedious and maybe arcane to some of the listeners, but I think it's important that we address these because they will come up later in the discussion in my estimation.

Now, first of all, a lot has been made in the presentation today about an imbalance in patients. I would ask the sponsors specifically how was USA-22 designed and how is it that you can design a randomized trial and not use a recognized prognostic factor in the stratification of patients. I'd like to know that, specifically the performance status. I don't believe this is a new prognostic factor.

DR. KREMER: Thank you, Dr. Johnson.

USA-22 was designed as an open-label and

randomized trial and it was randomized by a sealed envelope technique and randomized by center which at that time was a fairly standard approach. This trial was not stratified, as is noted, for ECOG performance status. We did in fact have discussions around that, and as is noted, the division had a suggestion that this trial would be best if it were stratified by performance status. Unfortunately, at the time that conversation and suggestion happened, the trial was about 60 percent enrolled, and at that point it was not possible to undertake a prospective stratification.

DR. JOHNSON: That's an explanation but you didn't define for me -- really the question I asked is why was that not considered in the design of the trial. You've explained why it might have happened, but I'm curious as to why that wasn't included in the design of the trial.

DR. KREMER: Sir, I think I can only state that these trials were designed around 1990. The appropriate prognostic factors were less clear at that time than they are now, and there still is not agreement in the literature on which is the set. At that time we did not stratify the trial up front for PS status.

DR. JOHNSON: Well, I'll just refer you to your own literature which you cite in your presentation which annotates those times where you in fact point to papers

where prognostic factors, including performance status, are stated as relevant to the design of these trials. I'm curious about that.

DR. KREMER: Yes, sir. You are correct and I would certainly say retrospectively that it would have been better had we stratified it, but at the time we put it together, we didn't.

DR. JOHNSON: I also want to address the issue of the landmark analysis that was performed which actually I think was addressed reasonably well by Dr. Scher. But as I understand the landmark analysis, that that has been proposed by Anderson, et al. in their 1983 paper, a selection of a landmark should be made before a data analysis is undertaken.

I'm unclear in my mind why the 8-week interval was selected for the landmark analysis. Much of your data and the data assessment and the response assessment took place at a different time. So, I'm curious as to why you selected 8 weeks for your landmark analysis, for the reanalysis of the data.

DR. KREMER: 8 weeks is a frequently noted landmark in the literature. I'd like to ask Dr. Ouyang from our statistical group to comment further.

DR. JOHNSON: While you're going to the

microphone, let me just reiterate a point you made during the course of your presentation in which you cite that 90 percent -- actually 87 percent -- of patients had demonstrated their PSA response by the 12-week interval. That would seem to me to be a logical time. Now, that's again after the data had been analyzed. I'm interested why the 8-week period was selected.

DR. OUYANG: In addition to what Dr. Kremer just mentioned, actually the way things happened is the liarozole USA-26 study was analyzed first, and in that study it was predefined that a patient needs to have at least 10 weeks treatment before they would be evaluable for PSA response. A lot of thought was given to that study, and based on the information we had at that point, 10 weeks treatment is deemed as the necessary length of the period of the treatment.

Coming out from that study, we are getting into the analysis for the two pivotal trials. Based on what we have learned from the liarozole USA-26, week 8 became a very logical choice and also it met with what Dr. Kremer mentioned earlier. That became the primary choice.

In addition to that, we also recognized the choice of the landmark may be an issue, so we have done the sensitivity analysis looking at the week 4 landmark, week

12 landmark, as well as the week 24 landmark to see whether the result is arbitrary to the selection of the primary landmark.

We also conducted a time-dependent covariate analysis which is not depending on the selection of a particular landmark, and that also supports the results.

DR. KREMER: Dr. Johnson, if I may ask Dr. Tsiatis to comment.

DR. TSIATIS: I'd like to comment just on landmark analyses a little bit, and that is basically what we do is pick a point in time, compare the responders and nonresponders that are available at that point in time, and then look at their subsequent survival. So, there are really two issues in the timing of where you pick the point, and that is, one, is there sufficient numbers that are responders and nonresponders that you can compare, and secondly, how many events you're going to see. So, if you pick it too far into the future, then you're not going to see subsequent events. If you pick it too far forward, you're not going to get enough responders and nonresponders.

So, where that cutoff is is somewhat -- there's this fuzzy area and that fuzzy area seems to be somewhere between 4 and 12 weeks. As Janssen said, they did it at

all of those times.

But I do want to mention that the most appropriate analysis, although difficult to understand, is the time-dependent covariate analysis which looks at the role of responders and nonresponders throughout all of time. That's the most appropriate analysis and that's the analysis that showed the largest difference between those two.

DR. KREMER: For the record, that was Dr. Anastasios Tsiatis. I regret that I did not mention it near to the microphone for recording purposes.

Dr. Scher, you had a comment as well I believe.

DR. SCHER: I think most of the points have been covered, but essentially the initial choice of the 8-week was based on the time of clinical reassessment. The first thing that was done with the raw data was to look at the patterns of PSA change and in fact, if you notice, at 8 and 12 weeks, there are still, quote/unquote, responders coming in. So, we're looking for the appropriate number of events.

We have as well done it at 8 weeks, 12 weeks, two points, three points, and used time-dependent with and without a landmark and get the same results.

DR. JOHNSON: I'll save my other comments till

the discussion later. Dr. Gelber was going to make a point.

DR. GELBER: Let me just follow up on the time-dependent covariate analysis. When other covariates were put in the model, did that influence the magnitude of the difference in PSA response?

DR. KREMER: Dr. Ouyang?

DR. OUYANG: In both the landmark analysis as well as the time-dependent covariate analysis that we have done, we've also examined whether the association coming out from those analyses can be attributable to other common causes. So, in doing that, we also added the baseline ECOG as well as the risk group that's coming out from the Cox regression model as the covariates.

After we have added that in there, the result is the association that was identified from those analyses are independent from the ECOG or the risk group that we have identified.

DR. GELBER: So, you get completely the same magnitude of effect associated with PSA response whether or not you put in other factors that might be associated with survival such as performance status, et cetera.

DR. OUYANG: Correct. The risk group is really coming from all the prognostic factors that have been

identified in the Cox regression model. So, those are the five factors, and based on that, we determined the linear predictor. So, that risk group is really accounting for all the prognostic factors, and adding that into the model does not change the association that we have established.

DR. KREMER: Dr. Gelber, those figures are in the briefing package for you on page 115.

DR. SCHILSKY: I just have a couple of other questions.

As I understand it, the eligibility criteria for the study were that patients were to have progression on primary hormone therapy. Can you tell us how progression on hormone therapy was defined?

DR. KREMER: It was to be defined in fact in the U.S. by the old NPCP criteria, and in Europe also similarly by clinical or radiologic grounds.

DR. SCHILSKY: So, have you, I guess in a sense, verified that the patients in the study actually were progressing at the time that they were enrolled?

DR. KREMER: We accepted the physician's note in terms of the fact that the patient had shown progression by the required criteria. We did not, for example, conduct a radiologic review of films at that time versus films that were existing prior to and not on study.

DR. SCHILSKY: Another question relates to -- one of the parameters in the Cox model I guess in the U.S. study was time since primary hormone therapy. I was just a little confused as to whether that means time from the beginning of the primary hormone therapy or time from the completion of the primary hormone therapy.

DR. KREMER: Dr. Ouyang, can you please comment on the factor for the Cox model?

DR. OUYANG: This variable was used in the liarozole USA-22. This is starting from the beginning.

DR. SCHILSKY: From the beginning, okay.

A question about the PSA levels again. Now, I believe you mentioned in your presentation that the studies were designed before PSA testing was widely available. So, I'm wondering then in fact whether baseline PSA values were available on all the patients for purposes of comparison.

You also mentioned that in order to be evaluable for PSA response, you had to have a PSA value greater than 20. So, that by itself would have dropped out some of the patients.

So, I guess the bottom line is were the patients who were included in the analysis of PSA response representative of the patients who were enrolled in the trial overall.

DR. KREMER: Thank you, and that's a very good question.

I do believe so and in fact we went and conducted the time-dependent covariate analysis for all patients making the assumption that any patient who was not evaluable for PSA response was a failure. When we repeated the time-dependent covariate analysis in that fashion, we still see the same advantage of the PSA responders over the nonresponders. So, I do believe that that holds.

DR. SCHILSKY: It would be nice, though, if you could show us the patient characteristics of the patients who were evaluated for PSA response and to show that those are not different from the patient characteristics of the population overall in the trials. Do you have that data?

DR. KREMER: You mean baseline demographics. I do not believe we have that available, sir.

DR. SCHILSKY: One other question with regard to the safety. It's quite clear that for the patients getting the liarozole, that skin problems and GI complaints are predominant. You made a comment about how it was likely that with better skin care and antiemetics and so on that these would be more tolerable. I take it that there was nothing in these protocols that recommended any particular types of management for these complaints.

But I'm wondering, in sort of the global experience that exists from these and other studies with this drug, whether you have any data to suggest that the incidence of these side effects is reduced or the severity is reduced if appropriate skin care and antiemetic therapy is in fact used.

DR. KREMER: Yes, thank you. Let me comment on that in two parts.

First, you are correct that in the protocols that we presented there was no prospectively planned either skin care or plan for antiemetic use. In fact, the antiemetic use in both LIA-INT-5 and LIA-USA-22 was quite low and in particular with regard to the potent antiemetics.

What I'd like to do in regard to management of these side effects and how we are proceeding with it, because we now do recommend particular agents for skin care and appropriate management of gastrointestinal side effects, I'd like to ask Dr. Dan Petrylak from Columbia and then Dr. Robin Murray from Melbourne, Australia who've treated patients if they could comment clinically on these events. These are folks who actually take care of the patients.

DR. PETRYLAK: I can comment on our two trials

that we're currently performing at Columbia. One is a trial of liarozole, three different doses randomized in patients with early stage disease, and a second trial is a combination of liarozole plus interferon for patients with refractory genitourinary malignancies.

In the first trial, we've entered 8 patients thus far and we've really seen only 1 patient with significant skin toxicities. We have been using vitamin E supplementation as well as the use of fatty soaps to help alleviate these problems with skin.

In our second trial, liarozole plus interferon, we've had 3 skin reactions in the 21 patients entered. Again, we are using vitamin E as well as fatty soaps. So, that seems to be helpful in reducing the skin toxicity.

DR. SCHILSKY: I'm sorry. What's the liarozole dose in your studies?

DR. PETRYLAK: The first trial is a randomized study, three different doses, 75, 150, and 300 b.i.d. It's blinded to the investigator. The second study is an escalating phase I study of liarozole plus interferon.

DR. SCHILSKY: And in that study where you seem to have more number of patients, have you gotten to liarozole doses of 300 milligrams?

DR. PETRYLAK: Yes, we have.

DR. KREMER: Dr. Murray from Melbourne, Australia has treated I believe in excess of 100 patients. I'd just like to draw on his experience for a minute.

DR. MURRAY: Yes. We in fact have treated more than 140 patients, and it's my impression that with more experience, we are able to counter these side effects more effectively. I think it's a very simple matter, as far as hypokalemia is concerned, to replace with potassium, and to treat the cardiac failure, if that occurs. The nausea and vomiting can be a problem, but with the use of antiemetics, that improves, or if it is intractable, it may respond to a dose reduction.

DR. SCHILSKY: Thank you.

DR. KREMER: Thank you.

I would just close by commenting, if you will permit, we are running as mentioned a new study. It's a factorial design which looks at liarozole either 150 or 300 with two doses of prednisone. It's really a large dose-finding trial, if you will. But this is one of the first trials in which we've had an opportunity to put these prospective arrangements in. At least at this point in the U.S., we have approximately 45 patients who are on 300 milligrams of liarozole, and so far the number of adverse event related discontinuations are low so far in the U.S.

on this dose. I realize and note that this is ongoing and this is tracking data, but I do believe that we are having an impact there.

DR. SCHILSKY: I have one other question again with respect to the PSA determinations. I don't believe you told us in the protocols how frequently was the PSA measured?

DR. KREMER: Monthly.

DR. SCHILSKY: It was measured monthly.

With respect to the response determination, the response criteria require a greater than 50 percent decrease from baseline on two determinations greater than 28 days apart. Are those two consecutive determinations or just any two determinations?

DR. KREMER: No, sir, and I should have been more specific. You cannot have a rise in the middle.

DR. SCHILSKY: Thank you.

DR. SWAIN: Could you discuss the compliance in this study?

DR. KREMER: In terms of dose taken?

DR. SWAIN: Right. In the booklet you handed us, I think in one of those studies it was 60 percent.

DR. KREMER: Yes, in terms of patients who remained on the 300 milligram dose. That's correct.

Both protocols permitted dose reduction in the presence of side effects, and that was used by most of the investigators and, as you note, in a fair number of patients. So, particularly in the international study, also it was possible to both dose reduce and then re-escalate. So, patients did spend varying lengths of time on 300 milligrams versus 150. I do believe I have figures on that if you will just give me one second to pull this up.

For example, in the LIA-INT-5 study, as you noted, the number of patients who remained at 300 milligrams for more than 90 percent of the time was 60 percent.

DR. SWAIN: Was that due to toxicity?

DR. KREMER: Our assumption is that dose reductions were based on side effects, yes.

DR. DUTCHER: Are there other questions?

DR. WILLIAMS: I would like to address my question to Dr. Scher.

I think it's widely known in the oncology community that responders do better than nonresponders in terms of survival, but it's not clear to us what that means. I don't think the community has widely accepted response as a surrogate for survival. In fact, I think

many of us believe that it is an independent prognostic factor maybe due to the patient's physiology, and as such you couldn't correct for it in a multivariate analysis and you couldn't correct for it with a landmark analysis because it's intrinsic to the patient.

Under such circumstances, the only way to prove it is to show that in all trials, that the two track and are never separated; that is, if you increase response in arm 1, you increase survival in arm 1. That would be a true surrogate.

Do you know of the track record for trials which increase PSA in one arm and do or do not increase the survival in that arm?

DR. SCHER: I'm not sure. You mean looking at patients who do not respond?

DR. WILLIAMS: Well, put it the other way, that arm 1 has more PSA responders and arm 1 survives longer than arm 2. That to me would be the true validation of a surrogate.

DR. SCHER: One way to do that -- I think if you impose different outcome measures, for example, look at 10 percent in one arm versus 20 percent, you'll see the shift in proportion of patients. We did that analysis looking at 10 percent increments and were able to show

above the 20 percent level, that there was a significant difference in outcome.

DR. WILLIAMS: I'm talking about between two arms, that is, that your treatment has increased the number of PSA responders and therefore the overall survival in that arm has thereby been increased; rather than it being a prognostic factor, that the PSA responders survive.

DR. SCHER: The only way we can do this on the validation set would be with the cyproterone where there was in fact a difference. Our data set does not represent comparative outcomes, so we can't do that.

DR. WILLIAMS: But in the literature recently, I believe there have been some trials where there has not been a tracking between PSA and survival at ASCO, and I don't have the specific --

DR. SCHER: The trial that you're referring to refers to a completely different population of patients, specifically those who have not received hormonal therapy who were hormone naive, as it were, and there's conflicting data in the literature as to the significance. I have not seen a final analysis of that study which is the INT-2 comparison of orchiectomy plus placebo versus orchiectomy plus flutamide.

This is a completely different population.

These patients are already hormonally suppressed. So, I think you may see differences in that.

Again, I haven't seen the final publication of that.

DR. SCHILSKY: One other question about the safety profile. Could you just comment again? I think this is in the submission, but I just don't remember the figures. But can you comment again what percent of patients in each arm of the trials began potassium supplementation during the course of therapy?

DR. KREMER: Started potassium supplementation or who were hypokalemic?

DR. SCHILSKY: Who started potassium supplementation.

DR. KREMER: We had not originally broken that out. We have gone back and done so, and so I can give you our counts.

In LIA-INT-5, potassium supplements were started during the course of trial by 17 patients on liarozole, of whom 12 appeared to be taking diuretic either prior or concomitantly. The figures for cyproterone acetate are 9 patients with 7 concomitant or with prior diuretic.

In LIA-USA-22, our figures show 15 patients on

liarozole who took potassium supplements, and 11 of those were in association with diuretic use. For the prednisone group, there were 10 patients who took such supplements and 7 of those were in association.

DR. SCHILSKY: I just want to be clear. Do these numbers reflect patients who began potassium supplementation while on therapy or patients who were taking potassium supplementation while on therapy?

DR. KREMER: These are patients who have potassium supplement indicated with a start date that is consistent with during the course of the trial.

DR. SCHILSKY: I'm not really interested in knowing about how many people had been taking potassium and then continued it during the trial. What I'm trying to get a handle on is is the hypokalemia that occurs from liarozole significant enough that it requires people to initiate potassium supplementation during their treatment.

DR. KREMER: Yes, sir, and my apology for not being, I think, clearer with my previous answer. The figures that we have are for patients who start taking potassium supplement during the course of the trial. I do not know what their serum potassium was necessarily at the time they started taking the supplement.

DR. DUTCHER: Are they also starting the

diuretics during the study?

DR. KREMER: Some patients did, yes. That is correct. Some patients were started on diuretic, and as I noted, in some cases the diuretic use was concomitant with the potassium supplement. As I say, I apologize. I do not have serum levels of potassium at the time those were done.

DR. GELBER: Yes. You have two multi-center trials that you presented and they used a sealed envelope method for randomization. We saw prognostic factor imbalances in the groups, surprising in a randomized trial. Were there any steps that you took to assure that the randomizations were conducted appropriately?

DR. KREMER: Dr. Ouyang, can you comment on our random codes and the randomization of the trials?

DR. OUYANG: This is regarding the liarozole USA-22 study where the baseline comparison seems to indicate more differences.

Your question is regarding whether we take any special steps to ensure the randomization at the starting stage.

Yes, as Dr. Kremer mentioned earlier, the randomization technique we used for those studies is based on the sealed envelope and that's per center. For each investigator, we have a separate randomization list. As a

result, the randomization is done at a site and then we have reported after the randomization was carried out.

The randomization was carried out okay, but the treatment assignment was not done correctly for 3 patients. In our analysis, those patients were attributed to the treatment group according to the drug they received. We also included in our analysis to attribute those patients to the randomization group they belonged to and the results were consistent.

However, to get back to the question earlier, there are some deviations apparently coming out from the trial. The deviations are captured from the analysis and we do not know how those things happened other than the apparent treatment misassignment and also more centers -- one more patient in the prednisone group than the liarozole group. So, that adds up. That's why there's a discrepancy in numbers in the assignment.

DR. GELBER: So, there are some centers with just 1 patient enrolled? Is that what you said?

DR. OUYANG: They end up with 1 more patient more in the prednisone group than in the liarozole group.

DR. KREMER: The study was blocked by center.

DR. GELBER: How many centers were there in the U.S. study?

DR. KREMER: Twenty.

DR. GELBER: And the international?

DR. KREMER: Dr. DePorre?

DR. GELBER: And one last question about that. Did you see the prognostic factor imbalances across all of the centers or did it seem to be attributed to just one or a few?

DR. DePORRE: For the international study, there were 54 centers all over the world. They were also having the sealed envelope system. There was in the end a balance, 160 versus 161.

DR. KREMER: And Dr. Ouyang, just with regard to Dr. Gelber's last question whether the imbalances were particularly concentrated in any center or were they distributed.

DR. OUYANG: In the liarozole US-2, we didn't really look into the per center prognostic factor comparison. We did examine the liarozole INT-5 and I will ask Tony Vangeneugden to comment on the findings there.

I will repeat the question just for the audience, whether the prognostic factor imbalances were observed in individual centers or not and whether there are differential prognostic factor imbalances among centers.

MR. VANGENEUGDEN: In the international trial,

we have about 54 centers treating patients. So, it's difficult to go into the centers separately, but we did go into the countries. That's what we usually do in Europe, instead of using centers, using countries. As you go to the smaller countries, there is a tendency sometimes to have an imbalance, but it's not a consistent trend.

DR. GELBER: Okay, thanks.

DR. KREMER: Dr. Gelber, did that adequately answer your question?

DR. GELBER: Yes. The reason for the question was the sealed envelope and the surprising imbalance. If one hypothesizes that the sicker patients might be the ones that one would argue should receive the new treatment, that there is a possibility of a looking at the envelope. I was wondering if you did some tests of the envelope or some kind of evaluation. Some of the answers were given do continue to raise concerns in my mind about whether that might have happened.

DR. KREMER: I know the question you're asking and I cannot definitively answer it. To our knowledge, there was no peek.

DR. DUTCHER: Mr. Anderson?

MR. ANDERSON: Yes, thank you.

Dr. Kremer, I had one question on the adverse

effects that you talked about. You mentioned the congestive heart failure as an adverse effect. Is that unique to liarozole, or do people who use prednisone or CPA ever have something like that to worry about, or is that unique to this new drug that you're proposing, liarozole?

DR. KREMER: Certainly. Congestive heart failure is not a unique event. I think let's put up the slide that I had before and I'll comment on it. So, if I can have the 4 carrousel back, please, and if you can give me slide 57.

The point at issue is that there is a somewhat increase numerically in the number of incidences of congestive heart failure in the liarozole arm versus the number on CPA and on prednisone. This is not a unique event, and there are certainly other drugs in which this is distinctly known as a consequence.

In these patients, as I mentioned, the occurrence of CHF was significantly linked with their baseline hemoglobin and it was also significantly associated with poorer performance status which I suppose is not surprising, and the performance status, as we've noted, was one of the imbalanced points.

We can't state whether this can have a component from a sicker population or whether it is drug-

related. CHF occurs in the general population in this age group and in the patient population in this age group. The occurrence rates that have been reported in various series are not very different from the rates that are present here on the slide. So, I can't definitively answer that and our position is simply that physicians ought to be cautioned that this has been observed and they should look for the signs of it.

MR. ANDERSON: But your slide does say that you got a 7 percent rate with Liazal compared with 3 percent with the other two.

DR. KREMER: That is correct.

MR. ANDERSON: So, it's doubled or better than doubled.

DR. DUTCHER: Are there other questions from members of the committee for the sponsor at this time?

(No response.)

DR. DUTCHER: All right, then we will take a 15-minute break and we'll be back here at 10:45.

(Recess.)

DR. DUTCHER: We're going to have the FDA presentation and it will include Drs. Honig and Chen who will present the clinical information and the statistical information. Thank you.

DR. HONIG: Thank you.

This is the FDA analysis of NDA 20-794 for liarozole. You've already heard the proposed indication for this drug earlier, so I won't repeat that.

I would first like to acknowledge the entire review team. It takes more than the one or two people that you see making the FDA presentations to evaluate an application.

As you've heard, the basis of this application is composed of three randomized open-label clinical trials with liarozole in patients who had failed hormone therapy for prostate cancer.

USA-22 randomized patients to receive either liarozole or prednisone, and 220 patients were included in the final analysis.

In the international study, patients received either liarozole or cyproterone acetate, and 321 patients were evaluable in the analysis.

Finally, USA-26 was a dose-finding study in which patients were randomized to receive one of three dose levels of liarozole, and 135 patients were evaluable for analysis.

In USA-22, the stated objectives in the protocol originally were to determine efficacy first as

defined by survival, time to progression, and response rates, and secondly, to determine efficacy as defined by changes in pain, performance status, and quality of life. The third objective was to evaluate the safety of this compound.

Patients received either 300 milligrams po b.i.d. or prednisone 10 milligrams po b.i.d. In the patients who were randomized to receive liarozole, there was first a run-in period where patients received 150 milligrams twice a day for 2 weeks before being escalated, and this was a run-in period that was derived empirically through earlier trials with this compound.

As we've heard from the discussion and the previous presentation, there was no prospective stratification in this study.

One significant amendment was made during the course of the study and that is that the definitions for response and progression were changed 10 months before the end of the trial. As you saw earlier in the sponsor's presentation, the original criteria involved fairly standard criteria for looking at measurable disease in bony lesions for both response and progression.

There was a clinical component to this as well. Patients could also be considered to have progressive

disease for anemia or obstructive uropathy. There was no criteria included in the original criteria for PSA definitions of progression and response.

When the criteria were amended, the same criteria for objective measurable disease in bone lesions were maintained. The definition of clinical progression was changed somewhat but was substantially the same. Anemia and obstructive uropathy were removed as criteria for progression and instead there were now put in place criteria for a PSA-defined progression, as well as PSA-defined response.

It's also important to note that most of the investigators used the NPCP criteria throughout the course of the study and that the amended criteria for response and progression were applied retrospectively after the close of the study to the patient population.

We've talked already about baseline prognostic factors in this study, and I would point out that there were factors that were statistically significant in favor of prednisone. However, we need to consider whether a factor is just statistically significant or whether it is also clinically significantly different between the two groups as well. In our analysis, the only clinically significant difference was the performance status, and I

would like to use the FLIC baseline scores as an example for that.

The FLIC is a 22-item instrument in which each item is scored from 1 to 7 for a total possible score of 154. A higher score means a better functional status.

The baseline score for the prednisone group, as you saw, was 118 compared with the baseline starting score of 111 for liarozole, so an absolute difference of 7 points.

The applicant cited literature in the NDA that suggested from published literature that an average difference of .5 point per item was considered to be a minimally clinically relevant difference. So, an absolute difference of 7 points over this scoring system works out to about .3 point per item so that I would argue that while we should look at the fact that these scores are different, whether they're clinically meaningful in terms of the way the patients marked their evaluations is another matter.

Patients received their assigned medication until there was evidence of progressive disease. In the original protocol, the primary analysis was specified as a survival analysis, which was presented in the study report. However, in addition, an adjusted analysis, which you've already seen the results of, was also presented and the

data were screened for 28 prognostic factors. The model was then derived to select five of these factors, and then the results were adjusted for this.

Dr. Gang Chen, as you've heard, from our Biometrics Division will be presenting after me and he will address this issue more in detail.

Finally, as was raised in the discussion session, patients were analyzed by the actual therapy they received rather than the randomized therapy which in part accounts for the apparent discrepancy in the numbers of patients on each treatment arm.

There were several issues that we identified in the analysis, including the use of the post hoc adjustment and the selection method for the factors. Again, this was not specifically prospectively outlined in the original trial, and Dr. Chen will deal with this further in his talk.

Again, while endpoints were identified, these endpoints were not fully identified in the protocol, in part because some of the changes that occurred during the trial and in part because again of lack of specificity. I'll come back to PSA in a minute, but time to progression, for example, was simply listed as time to progression originally and then with the changes in the response and

progression criteria near the end of the study, there's an issue with that being applied retrospectively to patients, but again it introduced a new element of using the PSA to define progression and response which then further amplified the way you might measure time to progression, as we've heard with the clinical PSA and radiographic component.

The response data, as you might imagine, was really not able to be interpreted. There were very few patients with measurable disease, and again that's typical of an advanced prostate cancer patient group where most people have bony disease that's evaluable but not measurable, and there were very few patients that had measurable soft tissue lesions.

In addition, although there was a prescribed schedule for follow-up testing, compliance with that schedule was very poor and many patients did not actually have repeat scans or have them on time.

Finally, an alternate method of bone scan interpretation was used by the central radiologist which makes it somewhat difficult to go back and look at progression in terms of the bone scan findings.

I just wanted to point out that in terms of PSA measurements, the original protocol simply measured the PSA

levels would be followed and analyzed but did not further specify the methods of analysis. The amendment gave specific criteria for determining a PSA response or progression and then these are the PSA parameters that were included and analyzed in the final study report.

I'd first like to talk a little bit about the changes in quality of life before addressing the main efficacy results. Quality of life was measured by a number of different parameters, including the ones listed on this slide.

The analgesic use was balanced between the two treatment groups at baseline, including when the potency of medication that was used for relief was evaluated. By about the second week, there was a statistically significantly better score for the prednisone patients, and this significant difference in favor of prednisone persisted at each time point until the end of the study.

The MPAC pain descriptor scale is one of four scales that makes up the MPAC pain description. In accordance with the published literature, they're each published and described individually. There's no one global packet that sums that up.

For the pain descriptor scale, the baseline scores were comparable. Again, there was a significant

difference favoring prednisone that was evident by the end of the study.

In the FLIC, the baseline differences were statistically significant in favor of prednisone, although I've already talked with you about the clinical meaning of that. Again, from the graph that was shown during the discussion session, it did persist. The liarozole patients had a further decrement of a mean of 12.5 points from their baseline score compared to a decrement of 5 points for the prednisone group.

No difference in urinary symptoms was observed.

This slide summarizes the efficacy data and in the first line here you can see the unadjusted survival analysis. Patients treated with liarozole survived a median of 11.7 months compared to 15.8 months for prednisone. The hazard ratio was 1.48 and is statistically significant in favor of prednisone.

The second column shows the adjusted analysis that was presented by the applicant, and I'd like to point out here that the hazard ratio still favors prednisone, although it is no longer statistically significantly different.

If one stratifies these results for performance status, which was in balance between the two groups at

baseline, the hazard ratio of 1.39 and remains significant in favor of prednisone.

And time to progression follows the same general features. For this slide I used time to clinical progression as an example.

In the international study, the stated objectives of the protocol were to compare survival, time to progression, quality of life, and treatment tolerability, and to also look at the response rate in patients that had measurable disease.

Again, patients were randomized to either 300 milligrams twice a day of liarozole preceded by the run-in period versus cyproterone acetate, 100 milligrams po b.i.d. The first 2 weeks of the trial were blinded, but at the end of that time, the blind was broken in order to allow liarozole patients to undergo dose escalation and the rest of the study was open-label.

Patients were prospectively stratified by performance status and the only amendment to the protocol allowed prior use of cyproterone acetate for flare reaction during their first-line hormonal therapy. It's not likely that this significantly influenced the results of this trial given the generally low response rate to second-line therapy in this group.

The significant difference in the baseline prognostic factors was the distribution of the pain score at baseline favored cyproterone acetate.

Again, patients ere treated until evidence of progressive disease. The primary analysis was a survival analysis. The original protocol noted that prognostic factors would be evaluated if necessary, but no additional details were given about the adjustments. And the study report used the same adjusted analysis that we have already seen from USA-22.

Similar issues were identified in the review of this study, the use of post hoc adjustment, again the fact that although PSA was measured and reported on, it was identified simply originally as a PSA value. And again, not surprisingly, there were too few patients with measurable disease to be able to look at a response rate in this study.

As I mentioned earlier, the PSA was simply defined as a PSA in the protocol, and again the final study report analyzed a number of parameters that had not been prospectively identified.

In addition, one of the Australian centers changed its PSA assay midway through the trial, something that can certainly happen at any major hospital and is well

beyond the control of any of the investigators or the sponsor. It was somewhat problematic because it occurred part way through the study and, because of the change in the assay technique, necessitated a correction factor of 1.25 be applied to any values obtained after this date in order to make them comparable to values done before that date and presumably to values done at other institutions.

It was difficult to tell from the literature that the applicant sent me as to how that was derived. I would assume it's probably an empirical kind of analysis done internally.

However, this center accrued a large number of patients, and 19 percent of the liarozole patients and 21 percent of the CPA patients were treated at this center. Approximately a third of the patients on liarozole who had PSA-defined complete responses occurred in patients from this center, and their therapy brackets this change in assay so they had some levels done before the change in assay and then some levels done after that.

Similarly, about a third of the PSA-defined partial responses occurred in patients from this center, and again you can see that some of these responses span the change in assay. Some were done afterwards, which again just raises another question potentially about the

consistency of the PSA assays through this study.

In this study the quality of life, as measured by pain and analgesic use by the FLIC and by the urologic symptoms, was really not different between the two groups. The sponsor noted that there was this small difference in change from baseline that was not statistically significant. The pain and analgesic use scale is scored from 0 to 4 in whole integers, so I would agree that a change less than 1 is probably not relevant.

This is the efficacy data from this study. Again, the first column shows the unadjusted survival. Patients taking liarozole had a median survival of 312 days compared to 314 days for the cyproterone acetate. The hazard ratio was close to 1 and was not statistically significantly different.

The second column shows the adjustment from the five-factor model derived from screening the 28 prognostic factors. The hazard ratio is now decreased to .74 and becomes statistically significantly different.

If one looks just at performance status, which was balanced in the groups, again there's no difference, and the same trends are visible in time to progression.

As you have already heard as well, a question was raised by both the applicant and FDA about whether

possible antiandrogen withdrawal response might have influenced the outcome in the trial, but in fact the pattern of use was well distributed between the arms. The sponsor did a number of repeat analyses that really did not change any of the conclusions that we've seen.

I'd like to address very briefly some of the discussion that we've had about the use of PSA as a surrogate endpoint. I would first like to point out that from Dr. Kremer's and Dr. Scher's presentations, it appears that decreases in PSA are prognostic overall for outcome. As Dr. Williams said earlier, we've known in oncology for a long time responders in general do better than nonresponders.

I think the question is whether a decrease in PSA would be predictive of the clinical benefit of an individual type of therapy. In other words, does liarozole produce more PSA responders who then live longer than patients who had PSA decreases that were induced by either CPA or prednisone? Dr. Gang Chen has some data that will address that in the next presentation.

I think that this is also an important point to make, which is that we usually consider a surrogate endpoint when we have just that, no other data and we're trying to use a surrogate endpoint. Here we do have data

that was collected on survival and time to progression, and in some sense that forms our gold standard no matter what we may think or decide in the future about PSA.

Finally, I want to briefly discuss USA-26. The objectives were to determine the relationship between several doses of liarozole on the steady state serum levels of this drug and changes in PSA in the same group of patients and also to look at the safety.

Patients were randomized to receive either 75, 150, or 300 milligrams twice a day, and again if the patients were randomized to 300 twice a day, they had the same run-in period. It was not stratified, and the only amendment changed the PSA entry level criteria somewhat.

There was no significant difference in the baseline characteristics between the three groups. The applicant noted in the NDA that there was an imbalance in performance status in the subset of patients who had been on study for at least 10 weeks that favored the higher doses of medication.

Unlike the other two studies where patients were treated until there was evidence of progressive disease, this study mandated a 16-week trial period. However, only 39 percent of the patients completed the trial.

In the protocol, the primary analysis was defined as an intent-to-treat analysis, and in the study report, it was defined as the subset of patients who were on study for at least 10 weeks. As you can see here, that analysis excluded 41 percent of the population who had dropped out before that time. And the primary endpoint here was PSA response. There was no data collected on survival or time to progression.

In general, I think one can say from this study that the liarozole trough plasma levels were proportional to dose and that higher doses appeared to have a greater effect on the PSA levels, although this was nonsignificant.

When considering whether to approve a drug, of course efficacy is considered, but an equally important component of this is the safety of the drug. You've already seen the general side effect profile of this drug. I think another way of looking at the tolerability of this is to look at both the compliance and the dropout rate to see whether patients share the perception that it's a well tolerated drug.

In this study you can see that on USA-22, a third of the patients took less than 90 percent of the prescribed dose, whereas compliance was nearly 100 percent in the prednisone arm.

For INT-5, the numbers are fairly similar. 40 percent of the liarozole group took less than 90 percent of the prescribed dose, where there was a very high rate of compliance with the cyproterone acetate.

Finally, in USA-26, there is a significantly higher compliance rate, somewhere between 97 to 99 percent, depending on which individual arm you look at. While I don't have a definite explanation for this, I would suspect that it's related to the relatively short duration of therapy for patients in this group. Remember again that 41 percent had already gone off study at the 10-week mark.

Another way to look at the tolerability is to look at the dropout rate for adverse events. In USA-22, 30 percent of liarozole patients dropped out for adverse events compared to 19 percent of the prednisone patients.

For INT-5, the numbers were 22 percent versus 13 percent if one looked at adverse events alone. There was a group of patients who had a concomitant occurrence of both an adverse event and progressive disease which increased the numbers, although again you run into the competing issue of progression.

In USA-26, the dropout rate was 20 percent overall, but this slide breaks it down with the individual incidence figures for the doses. I think again you can see

that the lowest dropout rate is associated with the 75 milligram po b.i.d. dose and that as you start to increase into the 150 and 300 milligram dose ranges, you start to get dropout figures that look similar to the other two trials.

Again, there was a significant amount of nausea and vomiting for liarozole in both of these trials, but as you've already heard too, less than 2 percent of the patients received any form of antiemetic therapy for this.

Most of the skin effects were noted as well. Although again these would seem relatively mild compared to what we see and tolerate with chemotherapy drugs, again it suggests that they were distressing to the patients with the dropout rate and lack of compliance or the need for dose reductions, although again no prospective management strategies were in place at the time these studies were done.

The other thing that struck us as we reviewed this application were the incidences of hypokalemia and congestive heart failure. Those are summarized on this slide. The first column looked in general at any potassium value that was less than the lower limit of normal at an institution, which is perhaps not a very good way of looking at potassium.

This column, though, looks at potassium levels that were less than 3.0, I think a value that most of us or all of us would agree is clinically relevant in these patients. 7 liarozole patients had significant hypokalemia compared to 1 prednisone patient, and the numbers for INT-5 were 14 and 1.

This addresses the new use of potassium supplements: patients that came into the trial not taking potassium, but then a prescription for potassium was written for them during the trial. Again, you can see that the numbers are higher on both liarozole arms relative to the comparators. All of these numbers were derived from performing an access query of the databases and looking at that.

I have to say, to address an earlier question, that I looked a little bit at what the potassium levels were that prompted this new use of potassium supplements. These are not the patients that had these potassium values. In other words, not all of the K less than 3 patients are included in the new use of potassium supplements. They were patients who started to drop their potassiums that had ranges of 3.2, 3.3, 3.4 who were prescribed this medication prophylactically by their physician.

The next two columns show the incidence of

peripheral edema effects and the new use of diuretics.

I'd like to just go directly to the last column which looks at congestive heart failure in pulmonary edema incidence. Again, these values were derived from a database query. I believe that one or two of them I found either looking through the narratives that were included and at least one of them in a medication list. 10 liarozole patients compared with 3 prednisone patients had congestive heart failure and 12 liarozole patients compared to 4 CPA patients had congestive heart failure.

In summary, this slide shows you the unadjusted analyses for survival. I think that when the adjusted analysis has not been prospectively described in the original protocol and that the adjustments have been done retrospectively, that the purest and best analysis that we can look at are the unadjusted results.

To remind you again, the unadjusted survival analysis showed that prednisone was significantly superior to liarozole, that cyproterone acetate and liarozole were not significantly different, that the adjusted analyses showed that prednisone and liarozole were not significantly different, although the hazard ratio still favored prednisone, and that liarozole was significantly better than cyproterone acetate, a drug with uncertain benefit in

prostate cancer. Again, the adjusted analysis will be further discussed by Dr. Chen.

This slide again reminds us that the adverse event rate and the early dropout rates were higher for liarozole than the comparators and that the compliance was lower for liarozole than the comparators.

What I'd like to do now is introduce Dr. Gang Chen from Biometrics, and at the conclusion of his presentation, we'd be happy to address questions together. Thank you.

DR. CHEN: Thank you.

The statistical review will focus on two major issues. I also will focus on two comparator studies, the liarozole USA-22 study and the liarozole international 5 study.

Before the discussion, I will briefly summarize the sponsor's results, the sponsor's efficacy results for the survival endpoint.

Based on unadjusted analysis, for the USA study prednisone is a significantly better than liarozole, and for the international study, there is no significant difference between liarozole and the CPA. However, based on the sponsor's adjusted analysis, the survival difference becomes nonsignificant for the USA study and for the

international study, liarozole is better than CPA.

There are three major statistical issues regarding the sponsor's adjusted analysis and landmark analysis. The first one is whether the sponsor's covariate selection is appropriate. The second issue is regarding the robustness of the adjusted analysis. The third issue is about the validity of the landmark analysis.

First, I will discuss issues of covariate selection. Five factors were selected by the sponsor. They are performance status, alkaline phosphatase, time since prior chemotherapy, PSA, and hemoglobin. The selection was via three screening phases: literature screening, univariate screening, and multivariate screening. The stability of selection was assessed using bootstrap simulation. I would like to take a minute to explain to you what bootstrap simulation is.

Bootstrap simulation is usually used to assess the accuracy of a statistical procedure. For example, in this study, bootstrap simulation was used to assess the stability of selection.

Bootstrap simulation can be conducted in the following way. The actual trial data is used as a representative of the patient population. You repeatedly draw samples from the trial data, as we would draw jelly

beans from a jar and replace beans of each draw. You draw the same number of the beans as patients in your original trial and do this a large number of times. For each sample, the multivariate selection procedure is run. Then one tabulates the proportion of times each factor selected over this large number of samples.

In simple terms, the rationale for bootstrap simulation is that resampling does with a computer what an investigator would do in practice. If it were possible, one would repeat the trial.

Let's take a look at percentages of the selections for each baseline factor. Five factors were selected most frequently. They are age, hemoglobin, time since their prior chemotherapy, LDH, and PSA. Age was not considered by the sponsor. However, this patient population is very old, and I found that in this study lot, age is significantly associated with patient performance status and patient hemoglobin level. The relationship between age and the survival was highly significant. Age was also considered in Dr. Scher's study.

If adjusting for five factors selected most frequently, the estimated hazard ratio for the treatment effect is 1.58. It's a 95 percent confidence interval. It's from 1.14 to 2.21. The result is significant with a p

value of .0065, favoring prednisone.

Similarly, based on the bootstrap assessment, five factors were selected for the international study. They are duration of response, hemoglobin, performance status, age, and PSA. Among them, three factors were selected most frequently. They are duration of response, hemoglobin, and performance status. You can see the percentages of the selection are over 90 percent.

If adjusting for the five factors selected most frequently, the estimate hazard ratio for the treatment effect is .77. The confidence interval is from .59 to 1.01. This is not significant, with a p value of .062, favoring liarozole.

The selection we just discussed was based on a pooled group, that is, all the trial patients. To avoid the treatment confounding in selection, I also did the covariate selection based on either the prednisone group or the liarozole group. If using the prednisone group, only one factor was identified, which is hemoglobin level. However, if using the liarozole group, five factors were identified. The result of the selection is similar to that used in the pooled group. This indicates that due to strong prednisone effect on survival, small baseline imbalances had a minimal impact.

Let's look at the robustness of the adjusted analysis. I will ignore the impact of age first. We have adjusted the models on the vertical axis and hazard ratios on the horizontal axis. 95 percent confidence intervals for hazard ratio are presented using line segments with ticks on them. You may see from this slide all the confidence intervals of the hazard ratio are shifted to the right and most of them are not overlapped with the line of hazard ratio 1.

Model 1 is the sponsor's model. The estimated hazard ratio is over 1.3 and its low confidence limit slightly crosses the line of hazard ratio 1.

Since age was significantly associated with survival and prognostic factors such as performance status and the patient's hemoglobin level, so I just added age in each selected models. Then you may see from this slide all estimated hazard ratios are around 1.5, favoring prednisone, and their confidence intervals are not overlapped with the line of hazard ratio 1. This means the adjustment treatment effects are significantly favoring prednisone.

For the international study, the confidence intervals for the adjusted analysis are shifted to the left. However, all the confidence intervals are overlapped

with the line of hazard ratio 1 except for the sponsor's one. This is the sponsor's model.

I would like to demonstrate the changes of adjusted p values for a test of the treatment effect. You may see from this slide all adjusted p values for the international study are greater than .05, except for the sponsor's one which is .039. However, based on the bootstrap assessment of the sponsor's model, we got a p value of .054 which indicates again the false positive rate may be inflated.

In the next few slides, I will discuss issues on the landmark analysis. The sponsor conducted a landmark analysis to investigate the relationship between PSA response and survival. However, landmark analysis may not be valid for this study. The following are the issues.

The first issue is that pooling data for landmark analysis is questionable because the basis for pooling data is the assumption that there is no difference between two treatment groups. However, as demonstrated before, it's not true.

The second issue, if week 12 was selected as a landmark, there were over 50 percent of patients who were excluded. Let's take a look at who were excluded. Those patients who had significantly poor baseline factors were

excluded. I examined the relationship between exclusion and those five baseline factors which are adjusted by the sponsor. All the p values were less than .05. And liarozole patients had over twice the chance to be excluded than prednisone patients. The p value is also significant. It's .003.

Based on the above arguments, the interpretation of the sponsor's conclusion is limited and extrapolation of the results to the entire population is problematic.

This slide actually addresses Dr. Johnson's questions in part. The sponsor emphasized the survival benefit of PSA responders only. However, a majority of patients were PSA nonresponders. In this slide I will demonstrate to you the prednisone benefit on both PSA responders and the PSA nonresponders. The median survival time for PSA nonresponders for those prednisone patients was over 100 days longer than for those liarozole patients. For those PSA responders, the median survival time for prednisone patients was over 50 days longer than liarozole patients, although they are not significant.

Before my conclusion, I'd like to share the ICH/FDA guideline with you. It's stated in the guideline that in some instances an adjustment for the influence of

covariates or for subgroup effects is an integral part of the analysis plan and hence should be set out in the protocol. When the potential value of an adjustment is in doubt, it's often advisable to nominate the unadjusted analysis as the one for primary attention, the adjusted analysis being supportive.

My conclusions are efficacy conclusions of the trials should be based on unadjusted analyses which is fairly robust given the results of all adjusted analyses. Both trials failed to demonstrate a benefit attributable to liarozole for patients with advanced relapsed prostate cancer.

Thank you.

DR. DUTCHER: Thank you very much.

Now, does the committee have questions for the FDA reviewers?

DR. SCHILSKY: I have just a couple of questions. I just wanted to get some clarification. I guess it was in the U.S. trial that you said that the amended response criteria were applied retrospectively. So, since the amended criteria determined response primarily based on PSA, then I would conclude that using the retrospective application of the response criteria that therefore not patients were evaluable for response because

not all patients had PSA levels?

DR. HONIG: That's right and there's a detailed listing of which patients were inevaluable for which particular PSA outcomes.

DR. SCHILSKY: And then related to that -- I guess this can start to get fairly confusing because as I could imagine this, the protocol had response criteria in it using the original response criteria, and the investigators who were following the protocol were treating patients until the time of progressive disease as defined by those original criteria. Yet, the analyses were subsequently done using the revised criteria which would have defined progression differently.

DR. HONIG: That's right.

DR. SCHILSKY: So, it seems to me that it's impossible to determine anything with relationship to time to progression because the people who are actually giving the treatment were using different criteria for determining progression and discontinuing treatment from the people who were actually analyzing the data.

DR. HONIG: Yes. For the few people that had objective measurable disease and were called on that basis, they translated well, and for the patients who were called a clinical progression translated well. But you're right.

Then there was this nebulous group who could either be classified -- I don't mean to speak for the applicant, but I think that's part of the reason that both clinical progression, radiographic progression, and PSA progression were looked at, and it wasn't one type of progression that was analyzed per patient to try to look at that.

Radiographic progression was also difficult because not everybody had bone scans done at the correct point, but all the patients who had a bone scan done at the 12-week restaging all had new lesions on bone scan. But there was a provision in the protocol to stay on study if the investigator thought it was in the patient's best interest, and from what I can glean, all of those patients stayed on. So, radiographic progression is also problematic.

DR. SCHILSKY: I had one question about the USA-26 trial. We haven't discussed that one very much because it wasn't a randomized trial, but I'm wondering if, at least in your analysis, there is any evidence of a dose-toxicity relationship. There were three dose levels in that trial and it would be nice to know if the incidence of the primary toxicities varied by dose.

DR. HONIG: Yes. I'm sorry I didn't bring that slide with me, but if you broke down things like the

hypokalemia and congestive heart failure, they're very small numbers as you might expect, but it does look like the 75 milligram b.i.d. dose has the smallest number. There's more on the 150 b.i.d. dose level. It's not clear to me that 300 was necessarily more toxic than 150 because of the small numbers.

DR. MARGOLIN: Yes. I have a couple of questions also referring to the same two points that Dr. Schilsky was asking about.

I don't recall from the original documents -- and I don't think it was presented today -- as to whether time to treatment failure, which is sort of a more global way of looking at why treatment fails, for example, coming off because of intolerance as well as progressive disease and other events, was looked at in these trials. It might answer some of the difficulties with the definition of time to progressive disease.

DR. HONIG: No, that wasn't looked at.

DR. MARGOLIN: And the other question was, since the sponsor didn't present 26 and you provided percentages, from what was given to us, it looked like the 26 trial had not completed its planned accrual of about 120 patients at the time of this submission. Is the data that you presented complete based on all 120 or so?

DR. HONIG: Yes. There were 135 patients that were entered and evaluable, so that was complete.

DR. GELBER: I had one question. You questioned the validity of the landmark analysis. Can you clarify for me what objective of the landmark analysis are you questioning its validity?

DR. CHEN: The issues about landmark analysis are -- actually this is based on only a subgroup of patients, and those patients excluded are those patients with poor prognostic factors. So, in this sense in terms of this, I think the landmark analysis is questionable.

DR. GELBER: What would you be using a landmark analysis to try to do, though? What's the objective of the landmark analysis?

DR. CHEN: The objective of the landmark analysis I think is to analyze like the survival difference between the responders and the nonresponders. However, like I discussed earlier, it's difficult to assess the responders if the time is too short. However, if the time is too long, then too many patients were excluded.

In general, I don't agree the landmark analysis is a good analysis especially for a trial like this because we don't know that group excluded are -- that group excluded is different from the group you analyzed. So, any

conclusion is very difficult to interpret.

DR. GELBER: Yes, I will grant you that, although it is a defined conditional analysis, that is, based on the status at whatever landmark one selects, do the patients who classify as responders versus nonresponders subsequent to that point do differently? Within that context I would consider the landmark to be valid. If you want to draw different conclusions relating to the entire treated population, then the landmark analysis is not an analysis that you would want to do because of that exclusion.

DR. CHEN: Yes. However, I think you need an assumption. The assumption is that the patients who are excluded should be similar to those patients left. Is that --

DR. GELBER: No, that's not an assumption that's made of a landmark.

DR. JOHNSON: Yes. I think this is again one of those nuances that confuses clinicians a lot of times in particular, Rich. If I understand this correctly, we can't make any decisions about the effectiveness of the therapy on the basis of the landmark analysis. Now, that seems patently absurd when you make that statement after you say that the responders live longer, but in fact it's a subset

analysis. It doesn't look the total database. I think that's an important element that often gets missed in these kinds of analyses and people walk away from meetings like these and say, well, they just ignored a "effective drug." You can't make that determination on a landmark analysis.

DR. GELBER: I absolutely agree with that. It's not designed to do a treatment comparison in that sense. Absolutely.

DR. DUTCHER: Dr. Gnecco.

DR. GNECCO: I see your point, Dr. Gelber, but I think that the slide that's very telling is the one that Dr. Chen had also giving you the other half of the picture and that was the nonresponder piece of it. So, I think that's a very important thing to look at.

DR. JOHNSON: So, it's a nonresponse analysis is what you're saying.

DR. GNECCO: Right. You need to look at both sides of the equation.

DR. DeLAP: If I recall the numbers, I think that when the exclusions were made, at least in the USA study, that patients that were kept in in the landmark analysis were more likely patients on prednisone than on liarozole. It's more likely that liarozole patients were dropped because they didn't make it to the landmark.

DR. CHEN: That's right. The liarozole patients had twice the chance to be excluded.

DR. JOHNSON: I've been asked to repeat the point I was attempting to make and that is that basically one cannot make a determination about the effectiveness of the therapy using a landmark analysis as the basis for making that determination. There are a lot of reasons why that is, but the principal reason is, at least in my mind, is it represents a subset analysis of the group of patients. It's not the whole patient population.

DR. GELBER: Just to further clarify it, that was the basis for my question.

DR. JOHNSON: Right.

DR. GELBER: The invalidity of the analysis is for treatment comparison.

DR. JOHNSON: That's right.

DR. GELBER: But if you have a different objective, then it's reasonable to look at it, but in this case it absolutely does not support the benefit of one treatment versus another.

DR. JOHNSON: It is truly ironic that a Georgia boy would try to explain to somebody from Boston.

(Laughter.)

DR. JOHNSON: I am a statistician to boot, but

that is what I was trying to do.

DR. MARGOLIN: My question is to the sponsor. Are we coming back to that?

DR. DUTCHER: Are there other questions for FDA?

(No response.)

DR. DUTCHER: Dr. Margolin has a question for the sponsor.

DR. MARGOLIN: I just have a question for Dr. Bush to please clarify your proposed question 4 because I believe you asked about, if we didn't approve this overall, whether we would consider it for a selected group of responders. I don't understand whether you're talking about people who responded to their prior therapy or to what group you are referring.

DR. BUSH: It was somewhat hard to hear your question, but I think you were just asking what we were -- say your question again, please.

DR. MARGOLIN: Maybe you could reiterate your proposed question 4, your added question to the committee.

DR. BUSH: Okay, can we get that up easily, or can we get that up?

DR. MARGOLIN: We may not need a slide. You may just be able to state it.

DR. BUSH: You want me to put it up, but you had a question about it.

DR. MARGOLIN: No. It may be that I just missed it the first time. If you could restate the question that you proposed to ask.

DR. BUSH: I believe it was if no to question 3, which you do have that in your book, it would be is there a subpopulation that could be identified for whom the risk-benefit ratio is acceptable and therefore warrants approval.

DR. MARGOLIN: Thank you.

DR. BUSH: That's all you needed, okay.

DR. DUTCHER: Are there questions from anyone else on the committee for either FDA or for the sponsor?

(No response.)

DR. DUTCHER: So, this is now open for discussion. We have our questions in front of us. The proposed indication is treatment of advanced prostate cancer in patients who relapse after first-line hormonal therapy. There are tables presented with the design of the studies showing the two primary trials: the U.S. study which was a randomized trial between liarozole versus prednisone with primary endpoints of survival and time to progression; the international study with a comparison of

liarozole with cyproterone acetate; primary endpoints, survival and time to progression. You can look at the data in front of you.

The first question is, is trial US-22 an adequate and well-controlled trial demonstrating the efficacy of Liazal in patients with advanced prostate cancer who relapsed after hormonal therapy?

Who would like to initiate a discussion of USA-22?

DR. SCHILSKY: Well, I'll start. I would have to answer that no. It seems fairly clear that this trial in particular was poorly designed without appropriate prospective stratification, and even if one goes through the re-analysis of the data, that I think in my mind is a very questionable thing to do, and stratifies by what I believe to be the most important prognostic factor which is performance status, the results still show that liarozole is inferior to the control. So, I would have to say no to this question.

DR. JOHNSON: I would just echo those comments. I think the reason that I read earlier the request of the FDA for validation of the efficacy of this drug was to indicate that in none of the instances that were put forward did this drug demonstrate efficacy. So, I would

agree with Dr. Schilsky. No.

DR. DUTCHER: Other discussion? Dr. Gelber?

DR. GELBER: I just want to raise a question for the committee about the PSA response and whether the clinical members of the committee could make some comment about that in this trial. I'm just looking for some shred of efficacy information as was requested by many of the speakers we heard earlier today.

DR. KROOK: I guess as a clinician I will try to answer that. Those of us in practice do follow the PSA perhaps not as the only thing, which many patients do. I think that the drug which is up has shown that it can drop the PSA and there are people who have had improvement in their clinical benefit. I suspect this can be demonstrated.

However, if prednisone is the control, then it is not as effective as others, and prednisone also showed improvement. One can say that both drugs showed that there were people who improved. I guess that's where the discussion enters, and you can discuss what the control is. We were here for the mitoxantrone/prednisone versus prednisone, so maybe prednisone is the control. At least that's my response as a clinician.

DR. SCHILSKY: I guess I would just add to

that. I think what I can conclude from this is that in about 20 percent of patients who take liarozole, the PSA goes down. Whether it goes down because of the liarozole, I'm not so convinced.

I think it seems reasonable to conclude that PSA response may be a prognostic factor for survival, but whether it is actually associated with the treatment or not is where I have a more difficult time drawing conclusions.

When you put the PSA data in the context of the trial, I'm also very impressed by the analysis indicating that even though it was not significant, there was a 4-month better survival for patients taking prednisone even among the non-PSA responders. So, again, it in my mind -- I don't know -- sort of uncouples the relationship between PSA response and outcome.

DR. GELBER: One other question. Was there any sense among the committee that prednisone was as good as it turned out to be in this trial before we saw the results of this trial for this condition? Is there any evidence that would indicate prednisone might be the treatment of choice?

DR. KROOK: Prednisone is used commonly, and oftentimes when we use it, we quit getting PSAs because this is about the third or fourth line. At least myself, I will sometimes quit looking and just see the patient and

not draw all these other laboratory tests at this time. I do use the drug but at that point drawing tests becomes less important than what the person feels like.

DR. JOHNSON: Yes. Let me remind everyone that we did look at the drug mitoxantrone last year in combination with prednisone and prednisone was the comparative arm. That was based on preliminary work that had been done by Dr. Tannick and his colleagues in Canada demonstrating benefit in terms of palliation of symptoms, not in terms of survival benefit, for patients who had advanced prostate cancer. So, those data I think do exist and have been validated subsequently in their randomized trial which was published at the end of last year.

DR. DUTCHER: Are we ready to vote? All those who feel that USA-22 is an adequate and well-controlled trial demonstrating the efficacy of Liazal in patients with advanced prostate cancer who relapsed after hormonal therapy? All those who vote yes?

(No response.)

DR. DUTCHER: All those who vote no?

(A show of hands.)

DR. DUTCHER: Eleven. So, it was unanimous, a vote of no.

The next question is regarding the

international trial. The data are presented in the table. Is trial LIA-INT-5 an adequate and well-controlled trial demonstrating the efficacy of Liazal in patients with advanced prostate cancer who relapsed after hormonal therapy?

Who would like to respond?

DR. JOHNSON: I think for a host of reasons this is a bit more difficult to deal with because of the adjusted analyses that took place by the sponsor. However, I think the answer to this question is also no. I think as was very nicely laid out by the FDA reviewers, when one looks at the analysis in a variety of ways, one comes up with a marginal statistical significance on just one type of analysis. Every other analysis clearly demonstrates a lack of statistical significance.

Even as a non-statistician but a clinician who takes care of patients, including patients with prostate cancer, it's very difficult for me to see a clinically significant difference in these data. I'm willing to accept the lack of the p value if I thought I saw something of clinical relevance here, and I don't see that.

So, I think personally the answer to this question is also no.

DR. SCHILSKY: Well, I would agree with that.

I actually don't find this particularly difficult to grapple with. In my mind I'm very comfortable accepting the unadjusted analyses for this trial. As the FDA pointed out, the only significant imbalance between the two arms was in the pain score, and I think that's a little bit questionable as to how important a prognostic factor that is.

So, this study was stratified by performance status I believe prospectively and the unadjusted analysis shows no advantage for liarozole compared to the control. So, I would have to conclude on that basis that the answer to this question has to be no.

DR. DUTCHER: Any other comments?

(No response.)

DR. DUTCHER: Okay, let's vote. Is this trial an adequate and well-controlled trial demonstrating the efficacy of Liazal in patients with advanced prostate cancer who relapsed after hormonal therapy? All those who feel that this has demonstrated the efficacy, please raise your hand.

(No response.)

DR. DUTCHER: No one.

All those who do not feel this has demonstrated efficacy, please vote. This is a vote of no.

(A show of hands.)

DR. DUTCHER: It's unanimous, 11 no.

And the third question, should Liazal be approved for the treatment of patients with advanced prostate cancer who relapse after hormonal therapy?

DR. JOHNSON: No.

DR. SCHILSKY: It's hard to disagree with Dr. Johnson.

This is fairly obvious but when you have two large-scale randomized clinical trials, neither one of which shows a clear benefit for the new compound in the primary endpoints, I don't see how it can be approved.

I would just also add that I'm not so convinced about the safety profile of this drug. It seems to me that there are some significant toxicities associated with it which can be very problematic for patients. It does cause nausea and vomiting. It does cause skin problems. While it may be true that we can find ways of dealing with those, it seems to me that from the patient's perspective, if they not only have to start taking pills, but then have to start taking anti-nausea pills and then have to start using skin creams, it's not so clear that this is a wonderful new therapy with respect to quality of life, particularly since it's not even so clear that the drug makes them feel better

in its own right.

Then, of course, there's the whole question lurking out there as to whether there is some increased risk of congestive heart failure and significant electrolyte imbalance. So, I think some more information ultimately needs to be gathered with respect to the safety profile of this drug.

DR. DUTCHER: Any other comments?

DR. MARGOLIN: I want to reiterate what Dr. Schilsky just said because I think in clinical trials we select patients for their ability to undergo the therapy. Unfortunately, this disease occurs in elderly men who have a lot of comorbidity and whereas those of us who are aggressive oncologists may think of a little congestive failure and hypokalemia and nausea as fairly minor annoyances and minor risks, these are going to be very big issues if the drug were to be used widely in the community for patients in this age group.

DR. DUTCHER: Then we should vote. Should Liazal be approved? All those who vote yes?

(No response.)

DR. DUTCHER: All those who vote no?

(A show of hands.)

DR. DUTCHER: It's unanimous, 11 votes of no.

Any further discussion? Yes?

DR. GIVEN: Can I address the committee on question 4?

DR. DUTCHER: Do we want to address the sponsor's request for a fourth question? No?

DR. JOHNSON: No. I don't think it warrants addressing under the circumstances. I don't see how we can make an analysis of any subset from the available data. I think it would be inappropriate to do that.

DR. GIVEN: Could I --

DR. DUTCHER: Would you like to make a -- sure.

DR. GIVEN: I very much appreciate this opportunity. I'm Bruce Given. I'm an M.D. I'm Vice President at Janssen responsible for R&D, as well as sales and marketing.

We requested having this fourth question added because we suspected that things might go the way they have today.

This is a really thorny problem, this drug. It has been around now in trials for about seven years, and obviously designing trials today, we would do things differently with randomization. Hopefully we would wind up with more balanced treatment groups and we'd have an easier time trying to make sense of what has happened here.

Instead, we have a situation where we did have more severe patients randomized to liarozole in the U.S. trial and we believe probably also in the international trial, although it was less clear cut.

As we heard today, there is still a good deal of debate over just what the important prognostic factors in prostate cancer are. There isn't even agreement amongst this panel, between the FDA and the sponsors, et cetera.

But I think that if we take a step back and try to take a look at what we've seen today, I think we've clearly seen that prednisone is an active agent. It produced PSA responses as determined by a greater than 50 percent decrease in about 25 percent of patients. Actually if you look at PSA response as defined greater than a 10 percent drop, it's about 40 percent of patients or so with prednisone. When they get that response, patients live for about a year longer. So, the drug is important. If we've done nothing but contributed that knowledge to oncologists and to patients and families, I think that will be an important point to make.

But what we've also seen I think is that if you look at PSA -- and I know there are a lot of questions about what's the value of looking at surrogates. But I think it's actually pretty important for physicians and

patients because, after all, on a patient-by-patient and physician-by-physician basis, you got to make decisions. If a patient comes in with hormone-resistant prostate cancer, there really are not options out there to be looked at. There certainly are not broad options. What you'd like to know is can you make some decisions and can you do something.

The reality is if the decision is that a patient wanted to try liarozole, the physician would know that after about an 8-week period, about 20 percent of the patients would have a decline in PSA of 50 percent or greater and if that happened, that that patient, if they stay on the drug, will live 9 to 10 months longer than if it doesn't happen. Frankly, if it doesn't happen, the physician can always make the decision at that point to try to grasp at some other straw. As you heard from some patients today, some portion of those patients -- and we believe it's about 20 percent -- actually do get that benefit from liarozole. It may very well be the last straw that they can grab at.

Now I would like to talk about tolerability a bit. The other thing that I wish I could turn back the clock and change is what Dr. Schilsky referred to and that is what we now know about how to prospectively deal with

the toxicity.

We now know and we've shown in trials and you heard from clinicians today who have treated in one case over 100 patients themselves that if you pay attention to it and if you use antiemetics judiciously and do things like avoid very drying soaps and the like, the dropout rate can be managed in much the way you manage every day to keep patients engaged with chemotherapy when they might otherwise become a bit discouraged. We simply did not know that during the conduct of these trials. We know it now.

With respect to the safety, again the same prognostic factors that were more severe for the prostate cancer were also prognostic indicators for CHF as well. But we're willing to worry that liarozole maybe does predispose to CHF and maybe does predispose to hypokalemia, and we believe, as long as we caution physicians, warn them to look for it, to treat it if they see it, that that's something that can adequately be handled in labeling.

So, what I would encourage the committee to consider is whether or not this product shouldn't be made available as the last course, which is what it is, for the end stage of prostate cancer with the guidance that it gets tried for a short period of time, and if the PSA responds, then the product should be continued and if the PSA does

not respond, something else should be tried. I think the data shows that. I think the data actually shows that for prednisone and cyproterone acetate as well and, if you ask Dr. Scher, probably several other agents.

That's really all I wanted to say. So, thank you very much.

DR. DUTCHER: Thank you.

Dr. Williams?

DR. WILLIAMS: I'd just like to respond. You mentioned that this should be tried as a last resort, but I believe that most of the data, if not all the data, are from one failure of hormone therapy and they do have another resort, which is prednisone. Is that correct?

DR. GIVEN: Yes. They had to have failed hormone therapy. So, I would agree that in this day and age prednisone is an option and an option that no longer can be viewed as simply palliative.

As I said, we know from our data at least that about 40 percent of patients will have some PSA response, about 25 percent will have a 50 percent response.

The other thing we have to keep in mind with prednisone is that some physicians are hesitant to use it until it's truly the last resort because you can't get patients off of it. Once you've suppressed their adrenals,

especially when they're in this state, you simply can't get them away from it.

But, yes, realistically -- and I guess you've approved mitoxantrone now too, but the options are still very limited.

DR. WILLIAMS: I guess I make the point because you're asking basically to base approval on a surrogate and we do do that for accelerated approval, but in general that's in the setting where there is no other option.

DR. GIVEN: Or very limited options. I think accelerated approval is used quite commonly, for instance, in AIDS where there are now many options. But it's really an issue of do you need more, and I think the answer here is there still are not enough options.

DR. JOHNSON: Well, I have actually several comments to make. I think some of the comments that were made were erroneous and they are based on, again, flawed analyses.

So, I think the comment that the response equals survival was not at all demonstrated in the data that were presented to us. So, frankly it may be true that that in fact is accurate ultimately, but that was not proved based on the data we were shown. So, in response to your first point, I think it's an opinion you have and I

understand why you hold that opinion, but you need to prove that fact. Number one.

Number two, this is not the study that demonstrated prednisone's efficacy. It has been demonstrated and there are publications, some of which you cited in your application, as far back as 1989 that are published data that show this. So, this is not new. You've not done a service to anyone by showing this because it has been shown before.

Thirdly, the ultimate cynic would say that what you've demonstrated is that Liazal actually is harmful to people, that in fact in you study you didn't demonstrate comparability, you demonstrated harm to the patient. You shortened their survival. Now, that in fact is one way one could analyze the data that you presented today. I don't happen to think that's in fact correct, but that in fact is one potential interpretation of the data that were shown.

Then lastly, as has been pointed out, the toxicity profile in a group of patients that your own group has pointed out has a short survival to engender 7 patients -- even 1 patient -- with congestive heart failure in the last days of their life I think is unacceptable. I don't understand how that can be perceived as improving quality of life.

Then lastly I would say none of your data -- none -- demonstrate any measure of improvement in quality of life.

So, I would disagree with everything you just said.

DR. DUTCHER: Well, I think we should stop.

(Laughter.)

DR. DUTCHER: We've voted. I think the data have been presented as they exist at the present time and we've had to make a judgment based on the data that was presented. Should new information come forth in the future, we will definitely be willing to reconsider and to look at it again, but I think based on what we were given to look at, the committee has voted with their hands and that's certainly the conclusion that we've drawn today.

I thank everybody for spending a lot of time and effort in looking at this very carefully and for the sponsor, as well as the FDA, in presenting the information that they analyzed.

With that, we're all going to lunch and we will reconvene at 1:30 for an open discussion of the new FDA guidelines proposed.

(Whereupon, at 12:07 p.m., the committee was recessed, to reconvene at 1:30 p.m., this same day.)

AFTERNOON SESSION

(1:33 p.m.)

DR. DUTCHER: We're going to get started. The afternoon session of the meeting is a discussion of the draft guidance documents that have been circulated and Dr. DeLap is going to lead that discussion.

DR. DeLAP: Thank you, Jan.

As I suspect most of the people in this room know, there were two draft guidance documents released by the FDA in March of this year that pertain to the evidence required, according to our current thinking, to establish the effectiveness of a drug or biological product. One of these guidances was a general guidance that pertained across the broad spectrum of drugs and biological therapies for different kinds of human illnesses, and the second was a corollary that spoke specifically to cancer drugs and new cancer treatment uses.

What I'm going to do today -- and our time is a little short because we've lost a couple members of the

committee and we're going to lose more with the afternoon flight schedules, so I'll try and move along fairly quickly and we'll want to get the committee input and discussion on several of the points as I go through.

I will be around, at least briefly, after the committee discussion has concluded, so if there are people in the audience that wish to address some comments to me, I'd be delighted to hear that, but I'd like to get through the discussion with the committee first so that people can get to their planes.

Again, the first of the documents provides a lot of interesting information about intent and background for these guidances. So, I'll draw from the first document for that information.

The second document provides examples of evidence again that can be used to demonstrate effectiveness of products used in cancer treatment. So, I'll draw from the second document for that.

The purpose of these documents. These are not really intended to be dramatic, new departures from our current practices. They are really intended to be documents that would elaborate and clarify what we think our current practices are. I think it's very important that we try and be as transparent as possible so people

know what we expect and again that's the spirit in which these documents are offered.

So, the first guidance was Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. Again, this is a more general document.

This is available for people who go on the Internet in the regulatory guidance section of the Center for Drugs' web page. So, it's www.fda.gov/cder.

This document goes into some of the legal background for standards of effectiveness. Of course, as I think just about everyone in this room knows, the legal standards that stated that effectiveness needed to be demonstrated before a product could be marketed date back to the 1962 amendments to the Federal Food, Drug, and Cosmetic Act.

I've just taken a few of the words that are found in the act and are cited in this draft guidance. "Substantial evidence, consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have."

Again, this is drawn from the act, so this is a little bit legalistic but it's a legal act passed by Congress.

These amendments have generally been interpreted as requiring at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. The act does not specifically say two or more studies. It's a little bit murky to discern the intent of Congress after the fact, but people who have studied this, and on occasion taken it to court, have determined that this is what the act means.

Now, as far as how the FDA has interpreted that, that's what the next two bullets pertain to. So, over the years, FDA has felt that you don't actually have to precisely replicate a study for the finding to be convincing, but you do need evidence at least from related studies that speak to the same benefits of the drug product. So, the term we've been using recently for that is "substantiation" rather than "replication" to emphasize again that what we're after is evidence that will show that the drug effect is real and we're not after simple replication of the result that you've already done once.

Again, the last bullet. In some cases FDA has accepted a single study generally when it can be regarded as self-substantiating or self-replicating I guess. This

has been in cases where there has been a single, well-designed, typically very large multi-center study providing highly reliable and statistically strong evidence of important clinical benefit and to conduct a confirmatory study would be problematic.

Perhaps the best examples of those are some of the large international studies of interventions in patients who've had a heart attack, for example. Some of those studies are extremely large and they come to statistically very strong conclusions. It would be very difficult to replicate. But we have also used that on occasion in the oncology area.

The act spoke to drug products. The agency has taken the formal position that biological products fall under similar expectations as far as the quality and nature of the evidence that is provided to establish effectiveness.

The scientific basis for the legal standard is the perceived need for independent substantiation of experimental results. A single clinical experimental finding of effectiveness, unsupported by other data, has not normally been considered adequate.

The importance of independent substantiation. Several points are noted in the guidance document. There

is certainly a possibility of bias which can be either undetected or conscious, and I don't mean to be pejorative when I say conscious. It may simply be that the investigator that's doing the study may strongly believe in the results and may see things that others would not have seen that aren't actually there.

Certainly a positive trial can occur by chance, a false positive result.

Site- or investigator-specific factors that are not recognized can produce results that turn out not to be generalizable to the intended population. So, what works at one clinic or hospital, even though it did genuinely work at that clinic or hospital, may not just work in another setting for factors that are unrecognized.

Again, finally and mercifully, extremely rarely in the cancer area in our modern experience, it is possible that apparent positive results could be fraudulent, again if they're not replicated or substantiated.

Other sections of this general draft guidance pertain to the quantity of evidence needed to support effectiveness and to documentation of the quality of evidence supporting an efficacy claim. Again, this is kind of a general discussion and pertains to all areas, not simply to cancer, and rather than going into this section

of the first draft guidance, I'm going to switch over the other draft guidance which pertains specifically to cancer and discuss some of the specifics from this document.

So, again the second document is FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products, and this is also available in the regulatory guidance section on the Center for Drugs' web page and can be downloaded and printed out. You can use the Adobe acrobat reader, which is very popular for web browsers.

So, this draft document, which I have a shortened title for now, describes the quality and quantity of data that may be adequate to add a new cancer treatment use to product labeling. Something I want to note specifically, the principles and standards that are described in this document are also applicable to establishing effectiveness of a new cancer treatment product. We don't regard the requirements for establishing a subsequent treatment use as being inherently less. We think that the requirements are inherently the same for establishing effectiveness. It's just that once you've got some data that establishes effectiveness in one setting, that may contribute towards making sure that you've got effectiveness in later settings.

So, we don't feel that we're differentiating between the initial NDA and subsequent supplements in terms of the level of evidence provided. It's simply that the priors, if you're a Bayesian statistician, can contribute to your confidence in later results.

Then at the end I'm going to say a few words about steps that the FDA is taking to foster continued updating labeling for products used in cancer treatment.

So, factors affecting the quality of data are required. Certainly what is already known about the product in terms of effectiveness and other related uses can be very helpful.

What is the new indication under study? Advanced refractory cancer settings. There are certain kinds of expectations for the nature of clinical data required and the quantity. There are different expectations for adjuvant or curative settings, and for pediatric use in a setting where drug is already approved for treatment of a similar condition in adults, we have a specific pediatric rule that pertains to that.

In addition as we're looking at the quantity and quality of data required to establish a new use of a product, we have to consider the availability and acceptability of other therapies for the condition in

question and we have to address the concern, have sufficient numbers of patients been studied so that we know enough about the drug to support approval of the new indication?

So, now I've got about five examples and I'd like to invite the committee to consider these examples and discuss and comment and give us a little feedback. Again, this is all drawn directly from the documents. So, if you have the document, you can see these things but they can all do with a little more discussion and elaboration and I'll be interested in hearing what the committee thinks about these things. So, again, it is a draft guidance. It isn't final yet, so it may still be modified and I'll appreciate comments.

So, for a product with established safety and effectiveness in a given type of cancer, a single adequate and well-controlled multi-center study may support labeling of the product for use in another biologically similar cancer. The example given here is aerodigestive squamous carcinomas.

So, the questions that arise from that in my mind at least that I'd like to hear what the committee would say: For example, if you have drug X that has been approved for a squamous set of neck cancers, does the

knowledge that the drug is effective in that condition give you sufficient assurance that it's likely to be effective in, say, squamous esophageal cancer or squamous lung cancer, and other upper aerodigestive cancers that you would feel one additional study would be enough to buttress that claim?

DR. DUTCHER: Arlene?

DR. FORASTIERE: Well, I would say no because I think that you can look at some instances where that's not the case. Say you look at the combination of cisplatinum and 5-FU. It has activity in head and neck cancer that's about double what it is in esophageal cancer. It's not an active regimen that's used for lung cancer. So, in squamous cancer of the lung, you wouldn't use cisplatinum/5-FU. So, I think there are differences in tumor types even though they may be of the same histologic type and related upper aerodigestive-wise.

Another example is adenocarcinoma of the distal esophagus. The taxanes were shown to be quite active in that group, but when they were studied in gastric cancer, not a lot of activity. So, I think that that would not be an appropriate leap to make.

On the other hand, I think if you have a product that has a track record and has been in use with

established safety and effectiveness, I'm not sure that this idea of a biologically similar cancer -- that you need another criteria. It would seem to me that if you had a single adequate, well-controlled multi-center study, that that in my mind would support labeling for use in another solid tumor, say. I would take out that "biologically similar."

So, I think you need to establish efficacy for each tumor type, but the issue to my mind is if you've got some history to that drug, people know how to use it, the side effect profile is well-known, that if have what you say, a well-controlled, multi-center study, in my mind that means a fair number of patients, that if you saw activity that the panel and the FDA felt was real and was supportable, then I think I'd be satisfied with that. I don't know how other people feel.

DR. DeLAP: I'm not quite sure I grasped exactly the distinction here. So, what you're saying is you think that it's treacherous to think that we know more than we do about --

DR. FORASTIERE: I wouldn't extrapolate from one cancer type to another for response data. Whatever is felt to be required or necessary to establish efficacy should be done for each individual tumor type, and this

biologically similar cancer I think is erroneous to think that you have biologically similar cancers because they share the upper aerodigestive tract or the lower GI tract and therefore response rates are going to be the same because we know that isn't the case.

DR. SWAIN: Can I just make a comment? I think what you're saying is basically if the drug has already been approved, you just need one study. So, you are going to look at efficacy in the one study. So, I don't see why there would be any problem with it personally, just having one well-controlled, large study.

DR. DeLAP: One other thing. The other comment I would make about the thinking here is I don't think it's our intent to say that there is a one-to-one concordance in terms of what works in head and neck cancers and what works in esophageal cancers. It's just that, again, it creates an expectation that if you've seen activity in the one setting, that it's more likely that your probability going in is increased that it's going to be active in the other setting. So, perhaps that information is an important addition in the background as you're considering the use of the new indication, but certainly not that head and neck cancer activity, for example, implies that it is definitely going to be active in another setting.

DR. SCHILSKY: Bob, I think one of the problems you have with this language is that the term "biologically similar" is a real moving target because it's not clear if that term refers to similar histologies. Would it refer to all EBV-related malignancies? Would it refer to all tumors with mutant P53? As the molecular biology of cancer is revealed more and more, it's likely that our definition of biologically similar is going to change from whatever it is now to something different in the future.

So, I would tend to agree with the comments that have already been made that I think that language might be fine if you just dropped out the term "biologically similar" because I'm not exactly sure how relevant it is. If there's a drug that's approved for a solid tumor and has a well-known toxicity profile and there comes along another adequate and well-controlled multi-center study in another tumor type, I think that might be sufficient for approval just based on that one study without having to suppose that the cancers are somehow biologically similar.

DR. MARGOLIN: I guess I would ask you to go back, if you haven't already solved this problem, to the other concern here that affects multiple ones of these marketed products questions which is the adequacy of a

single, even multi-center trial at all if it's phase II. I think we see time after time, those of us particularly who work in cooperative groups and who go to these meetings, the importance of patient factors and selection bias in influencing the outcomes of studies which can show the same drug to be active at a 20, 30, 40, 50 percent response rate versus sometimes 0 or 2 percent. I think there are a lot of drugs out there that are being used without really rigorous demonstration of their activity. So, I think that arguing for either more than one large multi-center trial or a phase III trial of some sort would really be crucial in all of these regards.

DR. DUTCHER: Well, I think actually we saw the converse of this yesterday when we were discussing Taxol in Kaposi's sarcoma where they had safety data at a specific dose in solid tumors with a totally different toxicity spectrum than what was presented in KS which is a different patient -- that argues against. That's not biologically similar, but it argues that even in certain disease entities, you're going to have some problems with particularly the safety perhaps as well.

So, I think each tumor type is going to require -- it could support perhaps the toxicity profile, but if you have a special situation where the disease and the

underlying problems impact on the toxicity, for example, patients that have COPD that get a pulmonary toxic drug that in non-COPDers is not toxic, those things have to be taken into account.

So, I agree with getting rid of the "biologically similar" and I guess the question becomes the single study.

Dr. Krook?

DR. KROOK: I was simply going to say the same thing. I think it makes it easier for you, Bob, if you drop out "biologically similar." Then it makes it an easier statement to deal with.

DR. JUSTICE: We still have the legal consideration of the plural, adequate and well-controlled studies, that we have to deal with and this is one way of dealing with that. So, if we're just considering that we have one study, we're not following the law strictly.

DR. SWAIN: But the other issue is that you could give an accelerated approval if you were really concerned about toxicity like some of us were about the drug yesterday. If you really had one randomized phase III study that really showed toxicity and you were happy with, you might not need to do that and you'd have the data in another tumor type.

DR. DeLAP: I'm speaking for others since I've been at the agency only relatively recently, but I think the agency over the years has been very reluctant to back off from the substantiation or replication concept and has been fairly assertive about the need for the substantiation.

However, what has happened in recent years has been what I would call finer and finer slicing of indications such that when a drug was approved in past years for cancer treatment -- and I'm talking many years ago now -- typically there would be a whole laundry list of different kinds of cancer where it had been tested and found to have some activity.

More recently we've been very precise about saying, well, which cancer is it and which stage is it and exactly what setting can it be used in.

So, I guess I would interpret some of the comments that I've heard as you're saying that, well, once you know that the drug does have effectiveness in some kind of solid tumor treatment, again that does provide you with some level of assurance that it is active and it provides some substantiation. So, that's I think how I would try and reconcile the comments with regulations.

Any other comments on this one?

DR. GELBER: Yes, just one other comment. It seems to me then that this can be turned around, that is, if you've got evidence in one tumor type, then this is saying you can accept a single adequate, well-controlled study and look to that other tumor type evidence to provide the substantiation. That's what I'm understanding the intent of this to be, to get you over the legal hurdle of the guidelines. The requirement for substantiation can come from evidence in a different tumor type than the one for which this second approval is being sought.

DR. DeLAP: I would say I kind of emphasized the legal hurdle aspect, but I also don't want to lose the scientific expectation aspect, that you need to have enough information so that people sitting around the table here, when the drug product comes up for review, you can say, well, I truly believe that there has been enough evidence advanced for this product and this indication that I'm comfortable with it being labeled for that.

DR. GELBER: Not to belabor it too much but an operative word here is "may" support. That's at least the way I read this change. So, it allows some latitude but an opportunity to use one very well-controlled study in a setting where there's already experience with an agent and evidence to show efficacy in another tumor type.

DR. DUTCHER: It would be also helpful, for example, if the primary data was extremely compelling, to not have to go back to the drawing board and do another study, but in fact have a substantiation from a different study.

DR. FORASTIERE: Well, I think it gets back to the idea also of what is well-controlled, and if you've got a phase III study, of course it's going to be controlled. But when you're talking about a single phase II study, it's either got to have adequate numbers of patients so that those confidence intervals are not gigantic or a smaller number of patients but with a high response rate and a narrow confidence interval from that standpoint.

So, really it can't be black and white. It's got to be interpretable for the specific situation, and again I would think that the data that you can get from another tumor type really relates primarily to safety but not to efficacy. I really think that one should not make that leap and use that data on the fact that it's efficacious for ovarian cancer, that then it's going to work in breast cancer or some other tumor type. I really think you have to stand by what the agency feels is necessary to show efficacy.

DR. DeLAP: I think part of the genesis of the

words "biologically similar" was that we were trying to exclude certain kinds of data along the lines of what you're saying I think. Certainly if you had a drug that was a good leukemia drug, for example, and you were going to start using it to treat colon cancer, they're really such different diseases and such different kinds of drugs that may work in those diseases that it's hard to say that you could use experience causing complete remissions in leukemia as a backdrop against which you'd require less data or a single study in colon cancer.

DR. MARGOLIN: Another clarification question would be that it sounds like you're generally talking about non-accelerated mechanisms of approval for new uses for marketed products, that when the data are supportive enough, the use of a single adequate and well-controlled trial will also rely on the sort of corroborative surrogacy endpoints established in the original approval rather than in these phase II settings where you cannot demonstrate survival benefit since it's not a comparator trial and the clinical benefit would be not always built into that study, such as quality of life, et cetera, but may simply be objective partial and complete responses and their durability. Is that correct?

DR. DeLAP: So, you're talking about the

distinction between the regular approval and accelerated approval and the nature of the new evidence that you have that this could apply to the accelerated approval concept as well.

DR. MARGOLIN: That you wouldn't be quite as exigent in these cases that you wouldn't require demonstration of survival benefit or clinical benefit, which are the standards for the full approvals, in these new uses of marketed drugs which are going to be approved for full approval rather than by an accelerated pathway.

DR. DeLAP: Well, I think our perception again is that the standards are basically the same for new uses as for initial uses of a new product. So, I think we would still stick to our requirement for things like survival benefits or other tangible patient benefits for full approval, and if all that was available was response rate without compelling evidence of patient benefits, we would probably still use accelerated approval in that setting. But the concepts could be the same. It's just that the kind of approval depends on the kind of data that you have.

DR. SCHILSKY: Bob, let me just ask one other thing which is sort of definitional again. If the term "biologically similar" were left in there or if some other term were substituted -- I was thinking based on these

comments that in fact oftentimes what we might be interested in is to see whether a study for a new tumor type has been done in a similar patient population to previous studies for which the drug is already approved.

But if there's a definitional term in there, would that imply that the sponsor would have to provide documentation that they're meeting the definition? So, if you talked about biologically similar, if that were left in there, would you expect the sponsor to then start off a presentation by providing documentation that the disease for which they are proposing an indication is in fact biologically similar? Then you begin to get into a little bit of the eye of the beholder problem. So, it's tricky.

DR. DeLAP: Yes, it is vague I think. I'm glad we're having this discussion. You can talk about epithelial cancers as being biologically similar. You can talk about all solid tumors versus hematologic malignancies. So, there is a lot of eye of the beholder here.

My sense is we're talking around the same issue. It's just that I'm having trouble at least finding the words to express exactly how it is. In some settings you can say, well, we've got this activity in another cancer and that really makes us expect that it's likely to

be active also in this condition.

But I would not imagine that that would be something that would become a routine part of an ODAC presentation, that the first thing would be to say, well, we really think that colorectal cancer is just like esophageal and this is the reason why.

But perhaps something along the lines of, well, the drugs that are used to treat this cancer generally overlap substantially, not identical with perhaps, but they overlap substantially with the drugs that are used to treat that cancer and something to link the cancers together more closely than, say, solid tumors and leukemia, which again I think is kind of a great divide.

So, I think that we should go back and think more about those words "biologically similar" and what they mean and how to characterize better the discussion that we've had here.

DR. FORASTIERE: I really think it's bad terminology and I think it's just going to be very confusing and I think it can lead to some false assumptions.

I was just reading in the draft here because you have a longer sentence about this. I really think that this should not be in there where you say another

biologically similar form of cancer that is known to have a generally similar pattern of responsiveness to chemotherapy may support labeling for that additional form of cancer. It's just too many "mays" and too many "generally similar." I think the whole idea is bad, to tell you the truth.

DR. DeLAP: Okay. So, you think we should eliminate this one?

DR. FORASTIERE: Well, I think this whole concept of extrapolating from one tumor type to another is a bad idea, and I think that you can take safety data, but I do not think you should be saying, well, it's got efficacy in X cancer that's nearby anatomically and so maybe it's got activity. I would get rid of that whole notion.

DR. MARGOLIN: I think there are probably more exceptions to the concept in terms of what we know about cancer than there are cases that fit. Since you individualize so many other things about what you ask sponsors to do for documentation of efficacy and so many other variations, to use this as some kind of a unifying factor probably doesn't make a lot of sense.

DR. DUTCHER: You're trying to get around the issue of having to designate two pivotal studies I think. Maybe the other source of information -- I think safety

data you could get from other tumor types, but most of the things that I can think of that would go in for a second indication have more than one trial done. They may not be as rigorous as what would be considered a pivotal trial, but there may be a lot of supportive data that could be utilized to support the efficacy portion and then use some of the data that were approval studies for other diseases as the safety data.

But I agree with what's been said, that I don't think you can use tissue type to define efficacy in the different diseases. I think Kim is right. There are far more exceptions than there are real data.

I understand the dilemma. I think you could write that down and then we could see the data and just say, well, that doesn't work, and it would just put people in a bad spot.

DR. WILLIAMS: One problem is that the first line I think is sufficient, as noted earlier, that if you do have a large, single, adequate and well-controlled multi-center study, that could be adequate and it substantiates itself. So, in some way there's a problem with this because it could be adequate from the first line.

DR. DeLAP: Well, that's certainly true if you have a large enough multi-center study, then it can be

self-substantiating, and certainly we've taken that view in the past and could again.

I think that the rationale behind the multi-center words there was simply to express that we still have concerns about data from a single or one or two centers as being sufficiently generalizable to other centers. So, it is worthwhile, even in a single experiment, to have data from more than one center.

Well, if there's no further discussion on this one --

DR. SCHILSKY: Can I just say one other thing? I think we're all grappling with sort of what the intent here is, and it seems to me that if an application came in in a particular tumor type and the patient population being studied was well-defined and if the applicant could say, look, this patient population has the following characteristics that are very much in common with a patient population for which the drug is already approved and those characteristics may vary across diseases, maybe that's getting closer to what the goal is, to be able to define common characteristics across populations of patients so that you could have some confidence that a new study actually bears a relationship to a population in which the drug is already approved. Now, that doesn't necessarily

mean that they're biologically similar cancers.

Is that more sort of along the lines of what you're trying to get to?

DR. DeLAP: I think that's a good expression of what we're trying to accomplish here. Again, perhaps we haven't captured it, but if there's a way to capture it -- again, I don't want to get to the point of having so many ifs and wherefores and maybes that it's meaningless, but if there's a way to capture it, I'd like to do that.

DR. MARGOLIN: I think that will be for the days when we start defining tumors by the expression of certain biological parameters that are known to correlate. For example, if you had another disease that was characterized by a 1517 chromosome translocation and you called it 1517 disease, in addition to APL, you could approve ATRA for those patients even though the tumor histology is different. We're not there yet.

DR. FORASTIERE: I think the emphasis should be on how compelling the data is in the single study not on similarity of the study to another population or another cohort that has been studied in a different tumor type.

So, I think the emphasis is in the wrong place here, and I think you should think more about defining the fact that a single trial in an already approved drug for a

different tumor type that is really compelling would be acceptable as opposed to trying to box it into some kind of category that would match something else that has previously been done because again, when I look at your second paragraph here, you say that this might be acceptable in patients with another type of advanced, refractory solid tumor with a response rate endpoint and enrollment of sufficient patients, blah, blah, that that may be sufficient. Here you're talking about, okay, let's look at more characteristics of the population rather than any kind of biologic similarity, to use that phrase.

Again, I think that the emphasis is on the wrong part of this, and the emphasis really has to be on how compelling the data is that's being presented in this single trial knowing that there's already established safety data out there.

DR. DeLAP: So, you would say something along the lines of that a single compelling, adequate and well-controlled multi-center study could support labeling of product for use in another cancer and leave out the "biologically similar"?

DR. FORASTIERE: Well, something like that. The wording would have to be thought through, but something that really puts the emphasis on --

DR. DeLAP: On the new data.

DR. FORASTIERE: On the new data.

And you may want to include something there that says something to the effect that the safety of the dose and schedule being studied for this new indication is also similar to what had been studied before. To me those are the two elements: one, that there's established safety data for that dose and schedule that's being requested in this new tumor type, and two, that the data that they're showing you is really compelling.

DR. JUSTICE: I'd just like to emphasize something that Dr. Dutcher said before because we're really discussing this in the abstract and the statement itself is a bit vague. If we're talking about a single adequate and well-controlled multi-center trial, are we talking about a randomized phase III trial or are we talking about a randomized phase II or a nonrandomized study?

Assuming that we're talking about a randomized phase III trial, we don't usually initiate that trial without some phase II data that it's worth studying the drug in that disease. So, I think in actual practice we often use a phase II trial to support a phase III trial. It may not be the same endpoint, and I think that's really the key. For example, if the phase III trial shows a

survival benefit and the applicant wants a claim for survival benefit, you can't strictly use the phase II trial to show that, but you might have something else like objective response rates that are high enough to suggest that it's supportive. To me that's the key.

DR. DeLAP: Okay. Perhaps I'll move along then to the next one, and this is where I think Dr. Forastiere was reading down. It's slightly different than the one we just looked at. It says that for a product with established safety and effectiveness in a given type of cancer in advanced, refractory stages, a single adequate and well-controlled multi-center study with a response rate endpoint and enrollment to characterize the response rate adequately may support labeling for the new use.

Again, I don't view that as probably being a whole lot different than our current practices.

DR. SCHILSKY: I think that's just what we did yesterday for Taxol and KS. It would be consistent with what you have on the slide.

DR. MARGOLIN: Maybe I'm misinterpreting this but this actually sounds like you're using data from one cancer to approve it in a different cancer.

DR. DeLAP: It speaks to solid tumors, but it doesn't differentiate among different kinds of cancer.

That's right.

DR. MARGOLIN: I think this is an even more extreme example of what we just decided we --

DR. DeLAP: Our perception has generally been that the risk of bringing in new therapies for advanced, refractory cancers is fairly small in the sense that the cancer is so terrible that the risks of a new treatment can be tolerable even if they're fairly serious, and even if the benefit is fairly small, the product can be brought forth. So, in the public health sense, I think the risk of bringing forth a new therapy for an advanced, refractory cancer is less than, say, bringing forth a new adjuvant treatment for breast cancer where the potential for disaster, shall we say, is much higher.

You're right. It's more extreme in the sense that it's just saying any kind of solid tumor can be used to support any other kind of solid tumor, but the kind of indication that it speaks to is an indication where we feel that it can be appropriate to take more risks in terms of the kinds of products that we approve.

Does it make sense?

DR. DUTCHER: I don't think that paragraph says what's here, though. I think what this is saying is that a single well-controlled multi-center trial is sufficient if

there are data from other trials in solid tumors. This is saying if there's a single trial, then it supports labeling for use in another disease? Is that what you're saying?

DR. DeLAP: Obviously I don't have the full document in front of me, but I think this captures the intent of what's in the document in the sense that the additional data can be from other trials in other tumor types. I think that's what it says in the document. It doesn't say other trials in the same tumor type.

DR. DUTCHER: May be sufficient to support in terms of? I think it's still the same thing. In terms of safety more than efficacy. Right?

DR. FORASTIERE: Well, I agree. I don't like this either. I think I feel the same way about this as I did the previous.

DR. MARGOLIN: It asks more questions than it answers.

DR. WILLIAMS: Bob, I think there's one point that is not clear here and that is what kind of approval. I think we've had this discussion. The document just says approval and doesn't say what type. It implies to me that it's going to allow full approval, and I'm not sure that's how we interpret this. I wonder if you could clarify your interpretation.

DR. DeLAP: Yes. It's difficult to capture everything on these slides that are some of the subtleties of the document.

If you look in the footnotes of the document, I think it says that the kind of approval depends on the kind of data that you have. Again, if it's a surrogate endpoint, then that's the kind of data that gets you accelerated approval.

DR. DUTCHER: I think it gets back to what Bob Justice was saying too, though. If you have a single adequate, well-controlled multi-center trial, there's going to be a lot of preliminary data based on phase II. My interpretation of the intent would be or the comfort level that we would have is if you have this well-controlled trial that fits the approval and you have phase II data showing that there's efficacy and you have other studies that show that there's safety, then yes, one trial would be sufficient.

DR. DeLAP: So, does it get back to that compelling question?

DR. DUTCHER: It goes back to that compelling primary data in terms of response, perhaps even long-term data that people have, say, if something gets dredged up after 10 years, but it has been being used anyway and then

they do this multi-center trial that says, yes, it's true. Then you get the other data, and then you have safety data. That's easy. The question is what's the minimum.

DR. MARGOLIN: To me it just brings to mind drugs that are not specific anticancer agents for which this might make perfect sense but may not be at all what you have in mind, for example, the use of strontium 89 or aredia for the various bone indications that are currently I believe tumor-specific but perhaps there are certain biological features of the tumors for which they are approved that they share with other tumor types which would make this type of an approach quite appropriate.

DR. DeLAP: Well, I think a lot the comments are like the comments we had on the last slide, so if there are no other comments that people feel are necessary at this time, I'll just go to the next.

For a product with established safety and effectiveness in a given type of cancer in advanced, refractory stages, a single adequate and well-controlled multi-center study may support labeling of the product for use in an earlier stage of the same form of cancer.

The thing to note here is that it's quite possible or likely even that the labeling for the advanced, refractory stages may have been based on an expanded phase

II experience, of course. If we just choose, say, breast cancer as an example, if you have phase II expanded experience that has gotten you labeling for advanced, refractory breast cancer and then you want to come in with a front-line chemotherapy for metastatic breast cancer, this would suggest that a single adequate and well-controlled multi-center study might be sufficient for that.

The nature of the study would almost certainly be different. It would be a randomized controlled trial as opposed to an expanded phase II experience.

Are people comfortable with that after I've expanded on that?

DR. FORASTIERE: Yes. This to me makes a lot of sense.

DR. SCHILSKY: I think this is probably fine although how much earlier stage are you considering? For example, if you have a drug that's approved for advanced, refractory colorectal cancer -- say, 5-FU refractory -- and there was then a single well-controlled trial demonstrating its efficacy in the adjuvant setting, in a sense you could argue you're going earlier by a few stages, and would you be satisfied with a single trial under those circumstances?

DR. DeLAP: Well, what do other people think about that question?

DR. SCHILSKY: I think I probably would so long as the new trial was in fact a very well-constructed, presumably randomized trial.

DR. FORASTIERE: Yes, I would agree with that. Maybe you want to just specify that it has to be a phase III type of study, again because yesterday we got into this issue of historical controls. So, you might want to be more specific in terms of the nature of the well-controlled trial, but I agree with what Rich just said.

DR. SWAIN: I'd just like to reiterate that too because in breast cancer, for example, sometimes we do have differing results in the adjuvant setting. So, I'm a little bit uncomfortable with just taking one study. Certainly it would have to be very rigorously defined phase III large studies with enough patient numbers to make sure that you really have a true result. But I think it would probably be okay. I'm just a little uncomfortable with it.

DR. MARGOLIN: I agree with Sandy and, in fact, would probably go a little bit further. I think we all know of good examples of very well-controlled trials in the adjuvant setting that point in completely opposite directions from each other for reasons that can't be explained by trivial factors.

So, I think perhaps the study design would be

important if you were going to consider approving a drug that was active in advanced disease for the adjuvant setting based on one well-controlled adjuvant trial. You might ask for a trial that demonstrated the drug was superior to rather than equivalent to the standard adjuvant therapy, and if it was only equivalent, number one, you'd have to have a much larger trial, and number two, you might have to demonstrate either less toxicity or have another corroborative trial with the same direction of outcome.

DR. KROOK: The other thing, Bob, is safety becomes a different issue when it's more earlier stage. Safety issues are different in advanced versus adjuvant. I think it comes down to how do you define a single adequate and well-controlled -- that's the question you ask every time we look at a drug. Is this an adequate and well-controlled multi-center trial? That's a question you ask us almost every time.

DR. SCHILSKY: Actually there's an important corollary to Jim's comment which has to do with the duration of follow-up to obtain adequate safety data because, for example, a drug might be approved in a refractory disease setting where the average life expectancy of the patient population might be six months, and if you put that same drug in the adjuvant setting where

patients might be at risk for developing toxicity for years, you might not have an adequate safety database from the refractory disease setting because patients never got followed out long enough.

DR. GELBER: One comment is that we find that each specific situation we look at, the kind of definition of what we consider to be adequate and well-controlled will change. So, the assumption, therefore, in being able to accept single study evidence is that the highest standard be applied to what we consider adequate and well-controlled for that particular setting. With that caveat, I would say this is a reasonable guideline to allow the acceptance. It may support; that is, a single trial may support.

But then the definition of adequate and well-controlled really has to be specific for that particular indication that's being requested for all the comments that we've heard. Long enough follow-up, second tumor possibilities, things like that need to be considered in one setting where the data are not available in another.

I think it's reasonable to say a single study may support. We should not be required to have two studies when in fact the committee feels that adequate and well-controlled has been handled with one. So, in that sense, I think I could accept this recommendation.

DR. KROOK: The more I look at it, the more comfortable I become with it.

DR. DeLAP: Well, the other comment I would make is that our current practice of involving advisory committee members in each of our discussions with companies will continue. So, this is not something that we would plan to implement in ways that would not be familiar to you or totally different from your views certainly.

DR. SWAIN: I think in the endpoints, again just to emphasize, really the risk-benefit ratio has to be there. The toxicity could be a lot more. I could think of a couple of examples that we might not approve it. Even though it may look equivalent with large numbers, but toxicity may be higher.

DR. DeLAP: Okay. Shall I proceed then?

This is a synopsis of the so-called pediatric rule, and it's something that I at least have had a little difficulty in figuring out exactly how we can appropriately apply it in the cancer setting simply because I'm not sure what it means to say the same type of cancer in children and adults. My impression is that there are very few such instances and perhaps not any that we can really be fully confident about. Even a disease that occurs both in children and adults, acute lymphoblastic leukemia, it still

may behave somewhat differently, and I'm not sure that having evidence in adults is -- if we're treating the same disease in children, I think it may be different.

Again, it comes back to some of the conversation we've had about translocations and whatnot. I would be willing to bet that when we learn more about these illnesses, we'll find out that in fact a lot of these illnesses that are anatomically or microscopically similar in children and adults may have different mutations and different underlying biology. Of course, we know a lot of them do have different biology now.

But the pediatric rule does say that if you have a disease that seems to be similar in children and adults, then you really simply need to study the drug in children sufficient to establish the kinetics and the safe dose, and you really don't have to reestablish efficacy.

Again, I don't know about the applicability of this in our disease categories.

Any comments on this area?

DR. KROOK: Well, safety becomes a bigger issue. It's the longer term.

DR. DUTCHER: Actually I'm trying to think. We haven't had that many drugs recently, but when Judith Ochs was on the committee, she kept asking to see the data in

children before she could vote, and there was very little in terms of the pharmacology and the efficacy data.

But I certainly can think of some drugs that have very, very diverse outcomes in children versus adults. So, the data may be limited, but it better be compelling.

DR. MARGOLIN: And the safety data are particularly important because the spectra of what's acceptable in the different age groups is widely, widely different. Even if the drugs act the same way and cause the same toxicities, you may see them through a very different microscope in children versus adults.

DR. DeLAP: Well, the other plug that I would put in, since Dr. Ochs isn't here, is that we really do need to see more data on children wherever it's appropriate and feasible to do so. Again, in terms of public health, although a lot of cancers in children are treated much more successfully than cancers in adults, there's still a very compelling public health need, and we certainly would bend over backwards to work with sponsors who choose to try and develop their drugs for children.

DR. GELBER: Is part of the motivation for the pediatric rule that in fact there are relatively few cases, luckily, fortunately, and so to demand a full-scale efficacy evaluation would be impractical?

DR. DeLAP: I wasn't around at the time the rule was drafted, so I'm not sure what all the motivations were. But I think that the issue that the pediatric rule was trying to respond to is that there are many drugs that are used in children which have not been adequately studied in children. I think a lot of it is outside the cancer area. Most, perhaps nearly all of it, is outside the cancer area.

DR. KROOK: Rich, the other thing in children that happens is that there's a much larger percentage, although they're smaller, that go on to clinical trials. I think that's true. That was one of Judy's things. Children with cancer -- there have got to be 40 or 50 percent of them go on clinical trials.

DR. DeLAP: I just thought I left a little ambiguity there when I was saying most or all of this was outside the cancer area. The motivation for the pediatric rule probably came from outside the cancer area.

DR. KROOK: So, I think within cancer, the kids have been looked at in many ways -- toxicity -- better than we adults have.

DR. MARGOLIN: This would be then an even greater example -- this is actually good news -- since there are a smaller number of pediatric malignancies and

probably a more limited cache of drugs that are used, of where the safety data from treatment of a different malignancy with the same drug can be imported for use in these approvals.

DR. DeLAP: For a product used to ameliorate adverse effects of cancer treatments, there may be concern that the product could also diminish treatment effectiveness. If such a product has established effectiveness in reducing adverse effects of a palliative treatment of one type of cancer without substantially diminishing treatment effectiveness, a single adequate and well-controlled multi-center study may support labeling of the product for use to reduce adverse effects in all similar palliative settings.

What's held back here is the notion that if you intend to use such an agent in a curative setting or where there's major benefit from treatment, one has to study the drug explicitly in that setting.

But what is suggested here is that if you have a drug that, for example, reduces the side effects of chemotherapy for advanced non-small cell lung cancer and you also study it, say, in advanced colorectal cancer and it also seems to work there, then you might be able to get that drug approved for all settings where the same adverse

experience is encountered.

An example would be a drug that, say, ameliorates bone marrow toxicity of agents, particularly, say, cyclophosphamide. So, you've got cyclophosphamide plus drug X. You have less toxicity. If you study that in two palliative settings where cyclophosphamide is used, then we could simply say this drug ameliorates side effects of cyclophosphamide used in any palliative indication.

DR. SCHILSKY: I think this sounds pretty reasonable. The only thing that I would want to think about further is oftentimes the approval of a drug that ameliorates side effects is related in some way to the dose and schedule of the drug whose side effects are being ameliorated. It's conceivable to me that such a cytotoxic compound might be used in different dose and schedule in different disease types.

So, the fact that a drug ameliorates the side effects in one disease setting with one dose and schedule might not necessarily be the case that it would similarly ameliorate side effects with a different dose and schedule of the drug. That's what I would think would require a little bit more thought.

DR. DeLAP: No other comments? I think I did try and put the most controversial ones first.

This is fairly straightforward I think. If you have a product that has established safety and effectiveness in a given type of cancer and approval of a new dosing regimen or use in a new combination regimen is sought, then a single adequate and well-controlled study can support inclusion of the new treatment regimen and product labeling.

It seems fairly obvious to me.

DR. DUTCHER: In the same disease?

DR. DeLAP: Yes. It's just to change the dosing administration details.

Those were the selected issues from the document. There are a couple of other points in the document, but I think they are less contentious and comments would be welcomed of course.

The document goes on to describe data sources to some degree and simply says that FDA has to be able to confirm the major study findings of course. Examples of data sources that may be required. The usual preference, of course, is that we have full study reports that include complete statistical analyses and individual patient data.

The document does go into some detail about options for other ways of providing us with the data that may also be acceptable. On occasion we have taken action

or at least considered taking action based solely on literature reports with fairly minimal additional data, but we've almost always had at least study protocols and details on what happened to individual patients of interest.

I don't really need any discussion on that point, but if someone has a comment, I'd be delighted to hear it.

Then finally, the document describes some initiatives that we are interested in taking at FDA to try and maintain updated labeling for products. Of course, as again most people here know, maintaining updated labeling for a product's use in cancer treatment is a big problem, and there is extensive use of products for indications for which they're not labeled. A lot of that use certainly can be appropriate, but we would prefer to have all of the appropriate information in the label, all of the information that's available about the appropriate established clinical uses that are based on data.

So, these are again initiatives that we intend to take to try and improve labeling particularly for older products. Surveys of the community regarding potential new cancer treatment uses of approved agents, regular reviews of product labeling by our staff, encouraging sponsors to

submit data where we see potential new applications for a product.

If there is a product that lacks an interested commercial sponsor, then we'll have to try and explore what other mechanisms might be available to maintain updated labeling. Of course, this becomes a problem with many older products that have gone generic and for which the commercial sponsor has little incentive to expend very much resource.

Then finally, we'll track our efforts to maintain this updated labeling.

Those are all the comments that I had, and I'd welcome any other comments that the committee may have or other thoughts.

DR. SCHILSKY: With respect to the initiatives, I'm just wondering what your thoughts are about the first one you had on the slide, surveys of the community. I guess I wonder whether in a sense that's really a cost effective way to find out information about potential new uses. It seems that it's likely that if there's something out there that is looking particularly promising, that it's going to end up getting presented at a meeting somewhere along the way and probably isn't going to be hidden. It strikes me it might require a fair amount of effort to

survey the community, and I'm not sure that what you're going to get back is going to provide you incrementally more information than what you would get from the other usual sources of information gathering that we have available.

DR. KROOK: I think it depends upon how you define community. You could define community as ASCO, whatever else, and I guess, as I see you've put it up, is the FDA going to make an effort to look at some of the national meetings or the publications and use that as community because that's where most of us get our information and talking from the actual community, the nonacademic places. What's in the labeling becomes important economically because a lot of my colleagues -- we haven't had a problem where I am -- have had insurance companies and others deny when it's not in the labeling.

So, when I look at community, I think if the FDA makes an effort to watch the peer journals, if that's community, the presentations and then add to this from there. So, I guess you have to define that.

I think going out and polling people what they're doing, you'll have a huge waste basket you can't interpret. There are people out there who use strange things, I'll tell you, and they should be denied.

DR. DeLAP: Well, I'm sure it's probably more attractive to our staff as well to be going out to the cooperative group meetings and participating and learning and bringing things back.

DR. KROOK: That's what I'm saying and kind of bring it back and take a proactive --

DR. DeLAP: Right.

DR. KROOK: -- not waiting for a sponsor to bring it and say, okay, let's put this in our labeling. If I look at this, you may be willing to go out or somebody may be willing to look at this and bring it back and say, hey, maybe we should add this and not wait for the sponsor to initiate it.

DR. DeLAP: Well, I think we do have some more ability to be proactive at this point, thanks to the PDUFA act. We have several more staff than we have had at times in the past, and so there are actually people that could be available to participate in meetings. And we are trying to do more of that actually. We see that as part of our job.

DR. KROOK: I have not really had problems, but I've listened at state societies as our colleagues have gone the way of looking to see what is approved. The FDA or actually what's in the PDR is looked at at one, but they've really gone to use other sources to try to document

this to third-party carriers. I think that my impression is that what goes into the book or otherwise rarely gets used because we, as FDA, are behind what's elsewhere, and there are some other groups that have taken that initiative when they're looking for this. That's getting into the economics of cancer, but that's important.

DR. GELBER: I had one other question. This is perhaps not really very politic, being that we're sitting inside the beltway. But when I joined the committee four years ago, there was a tendency to discount data from international trials and I've had a sense that that has been changing over the time. I'm wondering if there's any discussion in the guidelines about more modern approaches to using data from international trials.

DR. DeLAP: I don't think that we have an explicit discussion of that in either of these draft guidances. I would think that the reason for that might be that we don't really distinguish at this point in time. We think good data are good data, wherever they may come from. People do have responsibilities for conducting their trials in accordance with local regulations and the Declaration of Helsinki and those kinds of things, and we expect that. But aside from that, if it's good data, it's not so much of an issue where it comes from.

We have kind of a trust-but-verify approach, of course, and we do have to be able to still verify.

DR. KROOK: On international trials, you still have to look at the data or the case reports or the actual chart. That's harder to do. Am I right?

DR. DeLAP: Certainly we look at case records and patient listings, data, and we have auditors who will go and visit investigators in Italy or South Africa, or whatever.

DR. KROOK: Is it harder to get that information on international trials?

DR. DeLAP: There can be sites or investigators in the U.S. where it can be very difficult to get information.

(Laughter.)

DR. DeLAP: Well, thanks very much. It was a very helpful discussion.

DR. DUTCHER: Thank you.

Are we done? Anything else? I think we're adjourned. Thank you, all.

(Whereupon, at 2:46 p.m., the committee was adjourned.)