UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ONCOLOGIC DRUGS ADVISORY COMMITTEE

73RD MEETING

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WEDNESDAY,

DECEMBER 18, 2002

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The above-entitled meeting was convened in the Versailles Room of the Holiday Inn Bethesda, 8170 Wisconsin Avenue, Bethesda, Maryland, at 8:00 a.m., Donna Przepiorka, Chair, presiding.

MEMBERS PRESENT:

DONNA PRZEPIORKA, M.D., Ph.D. Chair
DOUGLAS W. BLAYNEY, M.D.
OTIS W. BRAWLEY, M.D.
JOHN T. CARPENTER, JR., M.D.
BRUCE D. CHESON, M.D.
STEPHEN L. GEORGE, Ph.D.
DAVID P. KELSEN, M.D.
SILVANA MARTINO, D.O.
JODY L. PERLUSI, F.N.P., Ph.D. Consumer Representative
BRUCE G. REDMAN, D.O.
GREGORY H. REDMAN, M.D.

ALSO PRESENT

KAREN M. TEMPLETON-SOMERS, Ph.D.	Executive Secretary
GEORGE BENSON, M.D.	FDA
SCOTT MONROE, M.D.	FDA
DANIEL SHAMES, M.D.	FDA
DONNA J. GRIEBEL, M.D.	FDA
MARK P. SCHOENBERG, M.D.	Consultant
PHILLIP M. HANNO, M.D.	Consultant
PETER C. ALBERTSEN, M.D.	Consultant
GEORGE H. OHYE	Industry Representative
JAMES ANDERSON	Patient Representative
ALEXANDER KRIST, M.D.	Consultant

A G E N D A

P R O C E E D I N G S

(8:06 a.m.)

CHAIRPERSON PRZEPIORKA: My name is Donna Przepiorka, and I wanted to welcome you to the second day of the Oncology Drugs Advisory Committee Meeting for a discussion of Casodex. For those of you who are new to this process, I just wanted to remind everyone that ODAC is not a policy-making or a decision-making body. We sit as consultants to the FDA, and the agenda for today will be an introduction from each of the committee members, a reading of the Conflict of Interest Statement, an initial open public hearing, presentations by the sponsor, presentations by the FDA, a second open public hearing, and then a discussion of questions by this committee regarding specific questions from the FDA before we adjourn later this afternoon.

And what I want to do is actually then start with the introduction of the Committee Members, and what we?ll do is just go around. If everyone will introduce themselves, Mr. Ohye.

MR. OHYE: George Ohye, Industry

Representative.

DR. MARTINO: Silvana Martino, Medical Oncology.

DR. PELUSI: Jody Pelusi, Oncology Nurse Practitioner and Consumer Rep.

DR. HANNO: Phil Hanno, Urologist.

DR. BRAWLEY: Otis Brawley, Medical Oncologist.

MR. ANDERSON: Jim Anderson, Patient Rep.

DR. KRIST: Alex Krist, Family Physician.

CHAIRPERSON PRZEPIORKA: Donna Przepiorka, Chief Malignant Hematology and Transplantation, University of Tennessee.

DR. TEMPLETON-SOMERS: Karen Templeton-Somers, Executive Secretary to the Committee, FDA.

DR. KELSEN: David Kelsen, Medical Oncology.

DR. REAMAN: Gregory Reaman, Pediatric Oncology.

DR. CARPENTER: John Carpenter, Medical Oncology.

DR. CHESON: Bruce Cheson, Hematology

Oncology.

DR. BLAYNEY: Doug Blayney, Medical Oncologist.

DR. REDMAN: Bruce Redman, Medical Oncology, University of Michigan.

DR. BENSON: George Benson, Medical Officer, FDA.

DR. MONROE: Scott Monroe, Medical Officer, FDA.

DR. SHAMES: Dan Shames, Director Reproductive Urologic Drug Products, FDA.

DR. GRIEBEL: Donna Griebel, Deputy Director, FDA.

CHAIRPERSON PRZEPIORKA: Thank you. Next Dr. Templeton-Somers will be reading the conflict of interest statement.

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made a part of the record to preclude even the appearance of such at the 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 and firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting with the following exception.

Dr. Sara Taylor is excluded from participating in today?s discussion and vote concerning Casodex. We would also like to note for the record that George Ohye is participating in this meeting as an Industry Representative acting on behalf of regulated industry.

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.

CHAIRPERSON PRZEPIORKA: Thank you. It is usually at this point that we have an open public hearing. Some participants have expressed the interest to actually hear the information presented by the Sponsor and FDA before making their comments. We have six individuals who have registered for the open public hearing, and four would like to speak at this time rather than wait until after the presentation, so I would call to the podium Mr. Bob Samuels from the Florida Prostate Cancer Network, Incorporated. And I would ask that each of the speakers for the open public hearing also please state your financial conflict of interest, if any.

MR. SAMUELS: Thank you very much and good morning. My name is Bob Samuels, and I would like to thank you for the opportunity to speak to you today as Chairman of the Florida Prostate Cancer Network, and actually on behalf of Casodex 150. We are a prostate cancer survival organization whose mission is to advocate the prevention of prostate cancer deaths in Florida. I appreciate the opportunity to speak about one of the most serious health problems facing

American men today, prostate cancer.

As you know, this year more than 180,000 men are expected to be diagnosed with prostate cancer, and over 30,000 men are expected to die this year from prostate cancer. Sad to say, prostate cancer has become almost epidemic among American men. In fact, last year prostate cancer was the most commonly diagnosed non-skin cancer in this nation.

Unfortunately, there is a segment of our population that pays a disproportionate price for this disease, and that is in the African American community. As many of you probably know, African American males have a 50 percent higher incidence rate, and die at twice the rate of white males in this nation.

I am an eight-year prostate cancer survivor, and a three-year throat cancer survivor. And in addition to being Chairman of the Florida Prostate Cancer Network, I am also Co-Chairman of the Florida Prostate Cancer Task Force, and I was the Founding Chairman of the National Prostate Cancer Coalition. I am on the Board of Directors of the

Moffitt Cancer Center, and I served on the NCI?s Prostate Cancer Progress Review Group. However, in 1992, I retired as Vice President of what is today J.P. Morgan Chase and moved to Tampa, Florida. And in 1994, I got diagnosed with prostate cancer. That set me off on a whole new direction in life, because I will admit that I had very little understanding of the disease prior to that.

Some of you may recall that earlier this year I testified on behalf of Casodex 150. Little did I know at that time that I would wind up within three months of that testimony actually being on Casodex 150. My PSA began to rise earlier this year, and it got to 9. Needless to say, when I consulted with my physician about what the next line of defense in my battle with this disease would be, he prescribed Casodex 150.

Had you seen me at 7:00 this morning, I was putting three little tablets in my mouth, and I do that every day in order to maintain a quality of life, and hopefully to stay alive until we can find that silver bullet that I hope is on the horizon, and

thousands of us who battle this disease every day.

You hear about the statistics, but my friends, I live with the faces and the voices every day of those men who are looking for some hope. They need all the weapons that we can come up with to give them hope, and hopefully keep them alive until we can find that silver bullet, so I would just urge you in your deliberation today to keep in mind the faces and the voices that the 30,000 men this year represent, and those who have already been diagnosed, and those of us who have been fighting.

Eight years I have been living with this disease. There are not a lot of options left currently in the arsenal of things that are available to me. This represents another weapon in that arsenal, and I can just once again please urge you, pass Casodex 150. Thank you.

CHAIRPERSON PRZEPIORKA: Thank you, Mr. Samuels. Next, Anthony Caputi from the American Foundation for Urologic Disease.

MR. CAPUTI: Good morning everyone. My name is Anthony Caputi, and I am the Manager of

Government Relations and Patient Advocacy for the American Foundation of Urologic Disease. I?m also a prostate cancer survivor, so I?m wearing two hats here. A couple of things first.

My organization does have a relationship with AstraZeneca, in that AstraZeneca does provide us with unrestricted educational grants for our educational programs. They also have paid some of my travel expenses that were incurred in order to review this data on two separate occasions. And also, I have signed a confidentiality agreement.

I?d like to read a statement that I prepared on behalf of my organization for Casodex 150. I?m writing to offer the American Foundation for Urologic Diseases', AFUD's, support of AstraZeneca?s application for Casodex 150 to be used as an adjuvant therapy of curative intent for patients with locally advanced, non-metastatic prostate cancer.

I am the Manager of Government Relations and Patient Advocacy for AFUD, and have been in this position for 16 months. This change in career direction began for me shortly after I was treated for

prostate cancer in March of 2000. I was diagnosed at the age of 43 with a PSA of 1.1. This unexpected mid-life crisis motivated me to utilize my experience as a very young man diagnosed with prostate cancer in an active way to eliminate the complexities of the disease, and work towards improved treatment, and an eventual cure. I, needless to say, have a keen interest in prostate cancer from both a professional and a personal standpoint.

I have carefully reviewed the data regarding Casodex 150, and am satisfied that this therapy has merit as an effective treatment choice for locally advanced, non-metastatic prostate cancer within the context of the clinical realities that prostate cancer patients deal with on a daily basis. Those of us that have been diagnosed with this disease are very familiar with our PSA readings. This FDA-approved blood test for the monitoring of progression of prostate cancer is not without controversy, but the truth is that many men are alerted to their disease due to an elevated PSA reading. And those of us that have been treated, continue to monitor our PSA levels

for the rest of our lives. This is the reality that we live with.

In the patient?s world, changes in PSA levels are the clinical indicators that guide a physician?s treatment and recommendations. As patients, any treatment that inhibits the progression of PSA, particularly for those of us who are at high risk for disease recurrence, is welcome with due consideration of potential side effects.

For the patient, prostate cancer is a complicated and confusing disease. Some men do very well with treatment, moving on with their lives and experiencing only transient side effects. A significant number of patients are not so fortunate, and find that their PSA levels are increasing at an alarming rate.

At this point during the prostate cancer journey, treatment options are limited, and side effects from the treatments for advancing disease can be very distressing to a man?s quality of life. The current standard of care for advanced non-metastatic disease is administration of an LHRH analog. The side

effects of this drug therapy include hot flashes, loss of libido and bone loss. For many, this disruption in quality of life is very distressing.

If Casodex 150 milligrams were approved by the FDA, this would provide an additional tool for the treatment of high-risk disease. To me, the data collected during the Casodex 150 trial phase is sufficient to warrant its approval. For the high risk patient, Casodex 150 appears to be effective in inhibiting the progression of prostate cancer as defined by the standard of care in today?s clinical practice; and that is, PSA monitoring.

The side effect profile offers certain quality of life improvements over today?s standard therapy, such as reduction of hot flashes, retention of sexual interest and function, and the preservation of bone mineral density.

In summation, the AFUD believes that the approval of Casodex 150 milligram for the indications under consideration is a good thing for patients as an effective agent for inhibiting the progression of PSA. This drug therapy offers an additional tool for the

doctor and patient to consider when faced with high-risk disease. In addition, the limited hot flashes, preservation of sexual desire and function, and the retention of bone mass are desirable for many men who find the side effects from currently approved treatments very difficult to bear.

I would like to thank the Committee for allowing me the opportunity to offer comments today, and on behalf of all prostate cancer patients, we appreciate your thoughtful consideration of this important matter. Thank you very much.

CHAIRPERSON PRZEPIORKA: Thank you for your words, Mr. Caputi. Next, Jan Marfyak from the Pennsylvania Prostate Cancer Coalition.

MR. MARFYAK: Good morning. This is an awesome group. I didn't expect to see so many of you here. As a former state employee of the State of Wisconsin, running a budget shop and subsequent to that, 23 years with the Department of Energy, I've conducted a number of hearings such as these over the years. I would point out that normally we allowed our people a good deal more time to speak than five

minutes.

I?m a prostate cancer survivor, and I?m currently Co-Chairman of the Pennsylvania State Coalition. In addition to that, I am working with the NPCC, National Prostate Cancer Coalition, in setting up state coalitions all over the United States. Furthermore, I also sit as an evaluator, consumer evaluator for the Congressionally mandated program at Fort Detrick that allocates roughly $85 million a year to the study of prostate cancer.

I am here as a supporter of this request by Casodex. They have paid my way from Gettysburg to come here. I?m going to be very short and to the point. You?ll have heard all these arguments later on, so I?ll be succinct in what I have to say. I?m neither a statistician, nor a pharmacist, and so I?m not equipped to address the numbers or the science involved in AstraZeneca?s study. But I can address the proposal?s efficacy from a consumer?s point of view. After all, they are the beneficiary of whatever you decide.

My feeling has been, in examining the

study that has been done here, that you?re talking basically about promise versus risk. As Tony and as my friend Bob from Florida have already stated, the consequences of prostate cancer are enormous, and until you?ve watched people die from this disease, watched the suffering that goes on, you really don?t have a full understanding of what?s involved. And anything that alleviates that, anything that creates a possibility is a welcome piece of ammunition in our arsenal to fight this disease.

On the other hand, there is a risk, always a risk. And as Tony has pointed out, there are a lot of liabilities on this. But if the patient has informed understanding of what?s involved, then this is something between the doctor and the patient to decide.

In the end, we weigh promise and risk, and if modality does no harm and there is a modicum of promise with the attendant risks, we view such a system or an outcome as a useful candidate for treatment. Our question is simply this, does this promise outrun the risk? We think it does. Thank you

very much for your time and attention.

CHAIRPERSON PRZEPIORKA: Thank you very much, Mr. Marfyak. I think our last speaker is Merel Grey Nissenberg from the California Prostate Cancer Coalition.

MS. NISSENBERG: Good morning. I?m Merel Grey Nissenberg. I?m an attorney in medical litigation issues in California, and I?m here today because my pro bono work is heavily concentrated in cancer and related issues. I also represent a very large constituency. I am in my fourth term as President of the California Prostate Cancer Coalition, which is a network of individuals, healthcare providers, and every support group for prostate cancer in the state. I am also the Co-Chair for the State Coalition Advisory Board for the National Prostate Cancer Coalition. I?m a CARRA member for NCI, and I?m the legal advisor to the Cancer Task Force in San Diego, so I come here to represent a great deal, a great number of voices in asking you to recommend approval of Casodex 150 in the proposed indications.

You should know that AstraZeneca has

helped to defray some of my travel expenses, but I have been privy to the data from AstraZeneca for nearly two and a half years, and I would not be here today if I did not believe that this would confer a significant benefit to prostate cancer patients.

Simply put, prostate cancer patients need every available option for treatment, plain and simple. Any new treatment or any new indication for an existing therapy that can be possibly beneficial for these patients should be encouraged. Since there is no 100 percent effective cure or treatment for any and all prostate cancers, why not add to the existing armamentarium of treatment modalities and give these patients a fighting chance.

While for many men the diagnosis of prostate cancer is clinically insignificant, for others it portends a future of untold suffering. Even with early prostate cancer, many men will go on to relapse, develop significant disease progression, and endure severe symptoms. So the question is, can Casodex 150 in the proposed indications confer significant clinical benefit to certain sets of

patients? We believe the answer is yes, we, the patients for whom I speak.

First, one must identify the specific subset of patients who would benefit. The trials showed that for high-risk patients who have ever undergone therapy with curative intent, or for those patients who are also high risk but for medical or personal reasons have chosen watchful waiting, Casodex 150 daily treatment resulted in an overall 42 percent reduction in the risk of objective disease progression. A time to progression benefit was shown, regardless of prior therapy at baseline, stage of disease, tumor grade or nodal status, and when pre-therapy PSA was greater than 4 nanograms.

Additionally, all three trials, all three trials showed a significant reduction in the risk of PSA progression, important because this is a clinical guidepost to the clinician. In everyday practice, this is considered a sign of biochemical recurrence, and therapy for recurrence is initiated at this point.

Second, one must ensure that adequate informed consent is obtained. The fact that there

have been side effects observed should not lead this Committee to recommend that the new indications not be approved. As long as a patient is aware of the risks of any side effects and still proceeds or wants to proceed, that should be a decision that, for him, the risk outweigh -- excuse me -- the benefits outweigh the risks of the Casodex.

Third, can a benefit for these identified subsets of patients be demonstrated? Trials 24 and 25 definitely showed benefit, both for therapy patients who had undergone therapy of curative intent, and as mono-therapy for those patients in the watchful waiting group. While Trial 23's results were not overwhelming, there are good reasons for that.

First, in the U.S. there was no watchful waiting group. There is no reason to think that the watchful waiting patients here would be any different than those in the rest of the world. Here is the main reason why we believe the results would be different, and why Trial 23 should not lead this Committee to vote against Casodex 150.

We believe that the results were immature.

Three years was not enough time for these patients to have benefits that would show up, because the majority of patients had an overwhelming number of good prognosis factors at time of diagnosis.

Additionally, the disparity in Gleason Grade should not be considered paramount, because number one, the Gleason Grade is only one of several prognostic factors that were shown in this regard. And the Gleason Grading in the U.S. was done on surgical specimens, not on biopsy specimens, which leads to an overall higher score.

Second, since most clinicians in the U.S. use PSA progression as a sign of biochemical recurrence, a lot of patients dropped out of the trial, or were taken out of the trial to initiate treatment for recurrence.

In conclusion, let me be the magnified voice of the prostate cancer patients, even those as yet undiagnosed, in urging this Committee to recommend the approval for the proposed indications for Casodex 150. The benefits in the trials bestow hope that the ravaging symptoms of advanced prostate cancer can be

forestalled, and perhaps never experienced. Thank you for your time.

CHAIRPERSON PRZEPIORKA: Thank you, Ms. Nissenberg, for sharing your assessment. Is there anyone else here who would like to speak at this time? In that case, I just want to say from myself and from the Committee that we are grateful to all these speakers that we heard this morning for coming and sharing with us your wisdom. Thank you.

I want to move on now to the presentation by the Sponsor on Casodex, AstraZeneca Pharmaceuticals. Introduction will be given by Dr. Kennealey.

DR. KENNEALEY: Good morning, Madam Chair, Members of the FDA Oncologic Drugs Advisory Committee. We are here today to present the Casodex Clinical Program in men with early prostate cancer. This morning we will show the data that will demonstrate the efficacy of Casodex in three large and distinct subgroups of men with early prostate cancer and earn your endorsement of Casodex for these indications. My name is Gerry Kennealey, and I am Vice President of

Oncology Research at AstraZeneca. I am a medical oncologist, and I have been associated with the Clinical Development Program for Casodex since 1987, when the Phase I clinical trials were first initiated in men with advanced prostate cancer.

We're here today because AstraZeneca has conducted the largest ever randomized clinical program in men with prostate cancer. As our data demonstrates, Casodex 150 milligrams significantly reduced the risk of objective progression in these men. However, the FDA issued a not approvable letter in June, because of lingering questions about the relevance of these data to U.S. patients, so today's presentation will answer the questions posed by the FDA in their Briefing Document.

With regard to these questions, we will show you that Casodex offers important long-term benefits to men with early prostate cancer. We will show that the men who derive benefit from Casodex can be identified without resorting to global standardization of Gleason scores. We have identified the men initially treated for curative intent with

either surgery or radiation therapy who will benefit the most from Casodex therapy, and we will show that the data from non-U.S. patients managed with watchful waiting can clearly be applied to U.S. men with prostate cancer. These data will demonstrate that Casodex 150 milligrams deserves to be approved.

Over the next hour or so we will present these data. Dr. Howard Scher is Chief of Genitourinary Oncology at Memorial Sloan-Kettering Cancer Center. Howard will discuss the need for new therapies, such as Casodex, in the treatment of early prostate cancer.

Dr. William See is Professor and Chairman of Urology at the Medical College of Wisconsin. He will concentrate his presentation of efficacy on the three subgroups of men for whom we are seeking your endorsement. Dr. See is a principal investigator in Trial 23, the North American Trial.

Dr. Mark Soloway is Professor and Chairman of Urology at the University of Miami, and Mark will then review the safety data and the relevance of Casodex to clinical practice in the United States.

And finally, I will return to the podium together with my colleague, Dr. George Blackledge and draw some conclusions from these data and resolve the questions posed by the FDA in their Briefing Document.

We have several external investigators with us today who will be able to help answer your questions. They are Dr. John Anderson, an investigator in Trial 24; Dr. Peter Iverson, who is the Principal Investigator in Trial 25; and Dr. David Paulson, who is Professor and Chairman of Urology at Duke University. In addition, there are a number of senior clinicians and scientists from AstraZeneca who will be able to address these questions as well.

Now I will begin with a brief clinical and regulatory overview of Casodex 150 milligrams in the treatment of early prostate cancer. Casodex was first approved in 1995 at the 50 milligram dose for the treatment of metastatic prostate cancer in combination with an LHRH analogue. In the seven years since Casodex has been on the market in the United States, and in 80 other countries, we have accumulated one million patient-years of experience, which means a

very comprehensive safety profile.

Casodex is orally bioavailable and has a half-life of approximately one week, and this permits convenient, once-daily oral dosing. Casodex does not lower testosterone. Therefore, when used as monotherapy, Casodex may avoid some of the side effects associated with castration, such as hot flashes, loss of bone mineral density, decrease in sexual interest and sexual function, and the debilitating weariness referred to as asthenia. This slide shows the rationale and design for the Casodex program.

Casodex demonstrated both single agent activity and activity in combination therapy in men with advanced prostate cancer. Investigators therefore followed the breast cancer paradigm with Nolvadex, which was shown to reduce the risk of disease progression by 36 percent, when compared to placebo in the B-14 Trial. They decided to look at the potential impact of Casodex in men with earlier prostate cancer.

As the endpoint of time to objective

progression has been accepted as valid by the FDA for approval in trials in hormonally sensitive cancers, the Casodex program was powered and prospectively designed to show a benefit at this endpoint.

This slide from your Briefing Document shows the extensive interactions that have taken place with the FDA over the last seven years, beginning with the agreement on the endpoint of Time to Progression in 1995.

The FDA in their Briefing Document refers to this as the sponsor?s endpoint. It?s not. It is a standard endpoint. It?s commonly used in clinical trials. It was agreed with the Agency in 1995, and it was the endpoint upon which we decided to embark upon this very large clinical trial program. The FDA's retrospective endpoint of time to bone scan progression was requested by the Agency in 1995, following the close of recruitment to this 8,000 patient study.

The actual objective of the program, as agreed in 1995, was to determine the benefit of adding Casodex 150 milligrams to standard care for patients

with early stage prostate cancer. Approval was to be based on Time to Progression, which was acceptable to the FDA if seen in more than one trial. Survival was also an endpoint of this trial, and the FDA acknowledged that survival data would be immature at the time of submission.

To satisfy FDA requirements, AstraZeneca undertook three complementary trials, prospectively designed for a combined analysis and stratified geographically, as quality data from throughout the world are acceptable to the Agency as the basis for approval.

In establishing the Casodex 150 milligram Prostate Cancer Program, AstraZeneca consulted with prostate cancer experts throughout the world. The Casodex program is briefly outlined on this slide, and Drs. See and Soloway will be reviewing the program in much greater detail. However, it?s important to note the following points. A total of 8,113 men with localized or locally advanced prostate cancer, were recruited in less than three years -- it?s a monumental achievement -- from 353 centers, in 23 countries. This

represents the largest clinical trial program ever conducted in this disease.

The next two slides cover some very important definitions for this trial program. Localized disease means that the cancer is confined to the prostate gland ? that is T1 or T2 disease, and locally advanced disease is defined as disease that has penetrated the capsule, and is designated T3 or T4 disease.

Other important factors as defined by the recent literature that would define patients at high risk for progression include high PSA at diagnosis, having a detectable PSA following primary therapy, or a higher biological aggressiveness as measured by a Gleason sum of 7 to 10.

Adjuvant therapy refers to therapy administered after curative intent in the absence of known, macroscopic, residual disease, and immediate therapy refers to the use of a drug, such as Casodex, the only therapeutic intervention for prostate cancer.

The actual indications that we are seeking

are outlined on these two slides. Casodex is indicated as adjuvant therapy to surgery or radiation therapy in patients with locally advanced prostate cancer who are at high risk for disease recurrence. And Casodex 150 milligrams is indicated as immediate treatment of localized, non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated.

To try and put it simply, this slide shows the patient subgroups we evaluated in this trial program. As Dr. Bill See will discuss, we are seeking an indication for adjuvant treatment following radiation therapy, adjuvant treatment following radical prostatectomy, and immediate treatment for men with localized disease. The original indications for Casodex, which we submitted last year, included locally advanced disease following watchful waiting.

As described in the briefing document, the FDA has concluded from the results of Trials 306 and 307 in men with locally advanced and metastatic disease, that an additional trial would be indicated for this indication. For this reason, we are not seeking approval for this indication at this time.

These definitions, as they relate to the subgroups for which we are seeking approval, are in the back of your binder, and we will be referring to them often throughout this morning.

Throughout our presentation we will be referring to a lot of figures, a lot of Tables, a lot of data, and Kaplan-Meyer curves. But as you heard from the Patient Representatives earlier this morning, we cannot lose sight of the fact that we are talking about men with prostate cancer, many of whom will develop symptomatic, metastatic disease.

More importantly, a new treatment option now exists. Casodex has the potential to delay the onset of serious and painful disease-related complications in men with prostate cancer. And now I?ll turn the podium over to Dr. Howard Scher, who will describe the unmet need for Casodex therapy in this disease.

DR. SCHER: Good morning. I?m Howard Scher, and I?m Chief of the Genitourinary Oncology Service at Memorial Sloan-Kettering Cancer Center in New York.

As a medical oncologist, I focus on advancing therapy for patients with prostate cancer. I?m involved in medical decision making for patients with localized disease, and the treatment of patients with more advanced and recurrent disease.

This slide shows what I?m going to discuss this morning. I?m going to demonstrate that patients with prostate cancer would benefit from additional treatment options. I will show where, in the spectrum of the disease, additional options are needed. The spectrum includes newly diagnosed patients with localized cancers who are at risk for recurrence, and patients considered for watchful waiting.

Prostate cancer constitutes a real and significant health care problem in the United States today. One hundred and eighty-nine thousand men will be diagnosed with the disease this year. Unfortunately, despite advances in treatment of early disease, many patients will fail therapy and die, Thirty-thousand men this year alone. These patients often experience severe and debilitating symptoms from their cancers, which results in a significant

deterioration in the quality of their lives.

Furthermore, patients who fail surgery or radiation suffer significant morbidity from the castration options that are currently available. This includes hot flashes, loss of libido and fatigue. So what treatments are available for men with early prostate cancer in the United States?

There are a number of options. A patient may elect to undergo therapy with curative intent by radical prostatectomy or radiation therapy. The choice is determined by considering characteristics of the patient?s cancer, their age, concomitant morbidities and preference. A patient may opt, or may be advised to defer treatment and undergo active surveillance, or watchful waiting, or a patient may elect to undergo castration-based therapies in the hopes of slowing the progression of their disease.

This slide summarizes data from six prostate cancer registries. It shows the frequency of use of the individual primary therapies for early prostate cancer in the United States. Radical prostatectomy is the most frequently chosen primary

treatment option. Radiation therapy is second, and hormonal therapy is third. But it is important to note that upwards of 20 percent of patients choose or are offered the option to defer therapy, otherwise known as watchful waiting, upon the initial diagnosis. And an additional 10 percent are treated with hormonal therapy alone. This group now accounts for approximately 31,000 patients per year in the United States.

This slide shows the spectrum of prostate cancer from diagnosis to death. It includes both newly diagnosed and treated patients in a disease continuum. Patients with clinically localized or clinically locally advanced disease are treated by surgery or radiation, but are at risk for disease progression to the state of a rising PSA. The risk of progression increases with the extent of the disease or T stage, the level of PSA, and the grade of the tumor.

Once the patient has reached the state of a rising PSA, he is then at risk for progression to a state of clinical metastasis. At this point, there is

a transition to the more lethal form of prostate cancer because the morbidity of the disease increases significantly, as does the risk of death from prostate cancer. The goal of therapy at any point in the illness is to prevent or delay progression to a more advanced state.

What happens when primary therapy fails? Typically, this is first manifested as a rising PSA. It is a sign that the cancer has not been cured. At this point, many men are offered castration. PSA progression is followed by objective progression on a bone scan or other imaging study. It is at this point forward that a patient?s quality of life deteriorates both from the disease and its treatment. It cannot be cured. The disease itself can cause bone pain, anemia, fatigue and/or spinal cord compromise. And the castration-based therapies that are currently available for PSA or objective progression are associated with unacceptable side effects for many patients. We clearly need better options to delay disease progression, and an option which we can discuss with our patients who are at high risk for

failure. So who are these patients?

The level of prostate specific antigen, or PSA in the blood, approximates the volume of cancer present. The higher the level, the more advanced the disease. For patients who are treated with radiation therapy, there is a higher risk of recurrence depending on the baseline PSA at the time the treatment is initiated.

As shown, patients with a baseline PSA level of 10 or more have a 60 to 70 percent risk of failure in just four years. The goal of treatment for such a high-risk patient is to avoid or delay disease progression. The same relationship holds for patients treated by radical surgery. The risk of progression increases with the level of PSA at the time of surgery. Unfortunately, many patients are not cured.

Patients who have a higher T stage pathologically assessed at surgery, are also at higher risk for progression to the state of a rising PSA. Pathologically localized T1, T2 tumors have a relatively low rate of progression at 10 years. But as the disease becomes more extensive, i.e., there is

penetration through the capsule or into the seminal vesicles, the risk of failure exceeds 30 percent at 10 years.

Now let?s focus on the 20 percent of patients who are treated with watchful waiting. What is the effect of no active treatment, and do these patients also need additional options? Watchful waiting is a conscious decision, or a formal recommendation to undergo no immediate therapy after the diagnosis of prostate cancer is established. These patients are felt to have competing causes of morbidity or mortality that exceed the risk of symptoms or death from prostate cancer, or wish to avoid the complications and side effects of radiation therapy or surgery.

These data are summarized from a series of databases of United States patients. The data demonstrate that there is a very consistent profile of patients who may elect to undergo watchful waiting. As shown, the age is generally between 70 and 74 years. Baseline PSA is about 6, and upwards of three-quarters will have PSA levels greater than 4. The

majority have moderate to low-grade disease, Gleason 6 or less. But despite our best efforts to select patients for watchful waiting, a significant percentage progress, and they do so within a relatively short time frame. These patients then require treatment to control the disease.

As is the case for patients who are treated with radiation therapy and surgery, the probability of requiring treatment within a 2 year (in orange), or a 5 year period (in blue), increases with the baseline level of PSA. These patients might be better served if there was a better-tolerated option to prevent or delay disease progression, thereby reducing the need for secondary therapy.

To summarize, the patients in need for additional options are: patients at high risk for progression after radiation therapy or surgery; patients with localized disease who are initially offered or who select watchful waiting. Both groups might be better served by immediate or adjuvant treatment. So is there a need for additional treatment options?

Prostate cancer represents a significant healthcare challenge. Radiation therapy and radical surgery is not curative for many men. These patients are at risk of objective progression, at which point their risk of death from prostate cancer increases significantly. Preventing or delaying progression can allow men to avoid the debilitating effects of their cancers. Castration, the only systemic option available at this time, is not acceptable to many men because of the side effect profile.

Watchful waiting is appropriate for some patients. It is widely practiced in the United States. These patients would also benefit from better- tolerated alternatives to prevent disease progression. So the answer is yes, there is a need for better options. Thank you.

I would now like to introduce my colleague, Dr. William See, who will present the Early Prostate Cancer Development Program for Casodex 150 milligrams.

DR. SEE: Thank you, Dr. Scher. Good morning. My name is William See. I am Professor and

Chief of the Department of Urology at the Medical College of Wisconsin. I?m speaking to you this morning as one of the Principal Investigators for Trial 23, the North American Trial.

Now I?ve been asked to address one minor housekeeping item. Dr. Kennealey alluded to some definitions that are used in this clinical trial, and we noted that you were searching your binders for those. Those are located on the outside of the back cover of your binder.

Now I?ve been an investigator in this trial program since its inception. Many of my personal patients are included in this trial, and I am intimately familiar with the details of this program, as well as the results.

What I will demonstrate to you this morning is a very robust effect of Casodex in reducing the risk of progression in patients with prostate cancer, an effect which is clearly demonstrated by the data, and these data strongly support the clinical benefit and use of Casodex for specific patients in this country with early prostate cancer.

I've organized my presentation as follows. First, I will review the objectives, the design, and the relevance of the EPC program. I will then demonstrate the efficacy results of the Casodex 150 milligram dose program, and I will place special emphasis upon those patient populations who see greatest benefit from Casodex in the EPC trial program. Specifically, patients at high risk for disease progression managed in either the adjuvant or the immediate therapy setting. And finally, I will summarize the data analysis of other clinically relevant endpoints.

The Casodex 150 milligram trial program was designed to answer a straightforward question. The program was designed to determine the clinical benefit of Casodex at the 150 milligram dose, administered as therapy in addition to standard of care for patients with non-metastatic prostate cancer.

Patients participating in this program constituted two principal groups. Those patients treated with curative intent with either radiation or surgery, or those patients being managed by watchful

waiting, in which the physician or the patient did not consider curative therapy to be a preferred option.

Our primary hypothesis was that Casodex would delay progression and improve survival relative to placebo in patients with non-metastatic prostate cancer, irrespective of their primary treatment modality.

The program consisted of three clinical trials, which were all randomized, prospective, double masked, and placebo controlled. The statistical considerations for the trial program are shown on this slide.

It was estimated that 7,500 patients would be required to detect a 15 percent reduction in the rate of progression at a minimum follow-up of two years. And importantly, the plan for a combined stratified analysis was prospectively defined in the protocols, and is justified on the basis that the individual trial programs were similarly designed and used identical primary, as well as secondary outcome endpoints.

As I?ve mentioned, the trial program

consisted of three different clinical trial protocols. And as you heard, these were conducted around the world. By design, these trials were designed to capture patients constituting the entire spectrum, if you will, of non-metastatic prostate cancer. While the overall design of each trial program was fundamentally similar, differences in eligibility criteria and prior treatment across the three trial programs were intended to capture the spectrum of early prostate cancer patients.

Trial 23 shown here was carried out in North America, predominantly in the United States. Patients in this trial treated with either radiation or radical prostatectomy were randomized to receive either two years of adjuvant therapy with Casodex at the 150 milligram dose, or placebo. Across the disease continuum, Trial 23 was designed to capture patients with earlier stage disease at a relatively low probability for disease progression.

Consequently, patients at high probability for disease progression were specifically excluded from this trial. These included node-positive

patients, or patients with a pre-treatment PSA greater than 20, if their nodal status was not previously pathologically defined. And in order to allow this to be a truly adjuvant trial, patients undergoing watchful waiting were not eligible for inclusion.

Now Trial 24 was carried out principally in Europe, and included patients at higher probability for disease progression. Included in this trial were node-positive patients, and those undergoing watchful waiting as their primary treatment modality. Patients in this study in the adjuvant setting received treatment for a duration of five years, whereas those on watchful waiting continued until the time of disease progression. And finally, Trial 24, carried out in Scandinavia constituted the other end of the disease continuum, and constituted those patients at highest probability for disease relapse.

To that end, patients at low probability in this trial were specifically excluded. And so, if you had a prostatectomy and your PSA was non-detectible, or your margins were negative, and consequently were at low risk, you were not eligible

for this trial program. Patients in Trial 25 received therapy until the time of disease progression.

There were two primary efficacy endpoints for this trial program. These were objective progression, which did not include biochemical relapse, and survival. Objective progression in this program was designed as disease progression confirmed by bone scan or other imaging technique, biopsy-proven local progression or death from any cause. In a specific effort to avoid any bias related to treatment effect from the active agent, all patients were required to have bone scans at two year intervals.

The second primary endpoint of this trial program was survival. I will tell you that given we only have three years of follow-up in this trial program, survival and prostate cancer in this trial is immature. Consequently, I?m going to be focusing on the outcome data for the primary endpoint of objective disease progression.

Now there were secondary endpoints shown here. Time to PSA progression, as we?ve heard from some of the initial speakers, is a disease-relevant

endpoint in this country. In U.S. practice, PSA progression is widely considered to imply primary treatment failure, and often serves as a prompt for the initiation or institution of second-line therapies. Additional endpoints included time to treatment failure, and finally, tolerability and safety, which will be addressed by the next speaker, Dr. Mark Soloway.

The baseline characteristics across the two arms of the overall trial program were very similar. However, not surprisingly, given the differences in the eligibility criteria between the three different clinical trial programs, there were some important differences in demography across the three trials.

Patients in the North American trial, Trial 23, were the youngest with a mean age of 64. In addition, they had the highest percentage of a minority group with 12 percent African American participation. They also had the highest percentage of treatment with curative intent, with 80 percent having radical prostatectomy.

At the other end of the spectrum, in Trial 25, in the Scandinavian trial, this was a very homogeneous population, the majority of which were managed by watchful waiting.

In the overall trial program, approximately two-thirds of patients have clinically localized disease, and few than 2 percent of patients had node-positive disease. However, patients in Trial 23 had the highest percentage of localized disease, 74 percent, and the lowest PSA was also noted in Trial 23. Here median PSA was 7.1, compared to 17.1 in the Scandinavian trial. These data suggest that patients at highest risk for disease progression were, in fact, in the non-U.S. trials.

There are some additional differences between trials in terms of Gleason scoring. Patients in Trial 23 appear to have a higher percentage of moderate to poorly differentiated tumors. Now you might justifiably ask why is this?

You will recall that the majority of patients in Trial 23 had pathologic definition of their Gleason sum based upon the fact that the

majority had undergone radical prostatectomy, in contrast to Europe and Scandinavia where the majority of Gleason scores were derived from biopsy specimens.

There?s also an interesting trend in the United States to upgrade Gleason sums. This slide is derived from the CaPSURE database of over 7,200 patients, and it illustrates what has happened over the last decade for the use of Gleason scoring in this country.

Over the past decade, we see a clear trend by pathologists to decrease the use of the Gleason range from 2 to 4, and to increase the use of intermediate to high Gleason Scores from 5 to 7. This does not reflect a change in the fundamental biology of prostate cancer, but rather reflects a grading shift among American pathologists in Gleason scoring. This shift, together with the fact that Gleason scores in Trial 23 were primarily derived from radical prostatectomy specimens explains the apparent disparity between Gleason score and other clinical indicators of tumor biology in Trial 23.

I?ve told you the EPC Trial Program

represents a broad continuum of the disease process we refer to as prostate cancer. It includes patients with relatively low-risk, early disease, such as the subset seen in Trial 23, as well as patients with higher tumor burdens, such as those seen in Scandinavia and Europe.

Now patients in Trial 23 represent a subset of the overall trial program with the lowest tumor burden as evidenced by their clinical stage and pre-treatment PSA. However, it?s important to recognize that Trial 23 is not only a subset of this overall clinical trial program, but in fact, represents a subset of patients with prostate cancer which we encounter and manage in the United States.

Conversely, Trial 24 and 25 included higher-risk patients. But here again, these patients are found not only in Europe and Scandinavia, but represent a significant proportion of the men we manage in this country. Based upon our knowledge of stage, PSA and primary therapy in those patients, we can extrapolate the results of the non-U.S. trials to U.S. clinical practice.

I would now like to share with you the efficacy results from the largest clinical trial program ever conducted in early prostate cancer. This is a very important slide. It illustrates the Kaplan-Meier plot for the prospectively defined primary endpoint of time to progression by the overall analysis. Remember that this trial was designed to detect a 15 percent reduction in the risk of objective disease progression relative to the placebo-controlled group.

Patients in this slide are represented by the orange line. What we see is a 42 percent reduction in the risk of objective disease progression associated with the use of Casodex. This 42 percent reduction is a highly statistically significant difference.

This slide illustrates the benefits of Casodex 150 milligrams for treatment groups according to their primary standard of care. Casodex reduced the risk for objective disease progression regardless of the primary standard of care, and this robust clinical benefit was observed for all groups. So

irrespective of whether you were treated with radical prostatectomy, radiotherapy, or watchful waiting, there was a statistically significant benefit in favor of Casodex for the reduction in the risk of objective disease progression.

Now there were some differences across the three trial programs for these endpoints. The largest difference between the two treatment arms was observed in Trials 24 and 25. In the North American Trial, Trial 23, we do not see a difference in time to progression between the two treatment groups at this point in time.

Remember though, these are the patients at lowest risk for disease progression, as shown by the low event rate in the placebo arm, and as evidenced by their pre-treatment PSA and clinical stage. This, however, does not imply something different about patients with prostate cancer in this country. In fact, some additional data I will now show you provides insights into the results of Trial 23.

Let?s shift for a moment from the endpoint of objective disease progression and look at the

effect of Casodex on biochemical failure for the overall clinical trial program. This Kaplan-Meier plot for PSA progression, with Casodex shown by the orange line, demonstrates a 59 percent reduction in the risk of PSA progression associated with the use of Casodex.

Interestingly, and in contrast to what we saw for the endpoint of objective disease progression, the effect of PSA on PSA progression was consistent and significant across the three trial programs. When we look at PSA progression, not only do we see a benefit in Trials 24 and 25, but now we see a statistically significant clinical benefit for patients enrolled in the North American Trial, Trial 23. This is an important observation.

In U.S. practice, PSA progression is regarded as treatment failure, and frequently triggers the initiation of systemic therapies, specifically hormonal deprivation. Consequently, as we?ve heard, a treatment that delays PSA progression is clinically relevant.

Even so, these data beg another important

question. Why do we see an effect in Trial 23 on PSA progression, but not an effect on objective progression?

I previously indicated to you that patients in North America often receive hormonal therapy at the first evidence of PSA, that is, biochemical disease progression. It appears that this was true in Trial 23. In Trial 23, five times as many patients in the placebo arm, as compared to Trials 24 and 25, had medical castration therapy introduced in the absence of objective clinical progression. This truly confounds our ability to interpret the effect of adjuvant hormonal therapy for objective disease progression in Trial 23. What, in essence, we?ve ended up with is immediate adjuvant therapy, or very early androgen deprivation therapy at the first evidence of biochemical progression.

Interestingly, one could argue on that basis that in Trial 23, the most interpretable and relevant endpoint could be an analysis of time to first progression, or the addition of second line therapy. This is the analysis that is shown on this

slide.

When we performed this analysis, now not only do we see a statistically significant effect in Trials 24 and 25, but now we see a statistically significant reduction in the event rate in Trial 23 in favor of Casodex.

Let?s return now to a discussion of the primary data from the EPC trial program. You will recall that the FDA has also asked these data to be presented according to an analysis of bone scan confirmed progression over the first two years of the trial. These data are shown here.

A highly significant reduction in the risk of developing bony metastasis was seen in the overall analysis, as well as in Trials 24 and 25. These data are consistent with, and support the validity of the primary protocol-defined endpoint of time to objective progression.

Therefore, what we have demonstrated from the data in the primary prospectively defined analysis is a significant overall effect on the clinically relevant endpoint of objective disease progression, a

reduction in the risk or progression irrespective of the primary treatment modality, whether it was radical prostatectomy, radiotherapy, or watchful waiting. And finally, a statistically significant benefit in two of the individual trials. But what about Trial 23?

In addition to the fact that patients in this trial constituted the lowest-risk subset for disease progression, the results of this trial have been clouded by the early use of second line hormonal therapies at a time when we do not see benefit for the primary protocol endpoint.

Consequently, although an overall treatment effect has been seen, we have to ask the question, who benefits most? And in truth, the FDA has asked the sponsor to specifically define the target patient population for this treatment strategy.

First, let?s consider the potential patient treatment groups and treatment settings. This slide demonstrates a matrix of potential treatment groups based upon either adjuvant or immediate treatment, and segregated by localized versus locally advanced disease. Let?s start by looking at the

adjuvant treatment setting.

This is the Kaplan-Meier plot for time to objective disease progression in patients with localized disease receiving adjuvant treatment. Although there is a trend towards a benefit in favor of Casodex, at this point in time the number of events are low. And consequently, the sponsor would not focus on this specific subset of patients. So while the current data does not support a use of Casodex as adjuvant therapy in patients with localized disease, I will now show you data strongly supporting the use of this treatment strategy in patients with locally advanced disease at high risk for disease recurrence following therapy with curative intent with either radiation or radical prostatectomy.

Let?s first talk about patients treated primarily with radiation therapy. Based upon the literature, patients at high risk for failure of mono-modality radiation therapy include those patients with clinically staged, locally advanced disease, and an elevated pre-treatment PSA.

Multivariate analysis of the data from the

EPC Trial Program confirmed the relevance of these factors in our trial, and subgroup analysis data that I?m now going to show you confirm that there was a marked benefit for Casodex in this specific subset of patients.

This is the Kaplan-Meier progression curve for high risk radiation therapy patients, defined as having locally advanced disease and a pre-treatment PSA greater than 4 milligrams. Patients in the Casodex arm are illustrated in the orange line. Overall in this high-risk group of patients, the use of Casodex reduced the risk of objective disease progression by 61 percent. This was a highly statistically significant benefit in favor of the active agent.

Let?s move on now to patients treated by radical prostatectomy. The literature suggests that those patients at greatest risk for failure of surgical mono-therapy are those with locally advanced disease, or a detectable post-operative PSA, or an elevated pre-operative PSA, or a Gleason sum greater than 7.

As was the case for the radiation therapy group, multi-variate analysis of data from our specific trial on radical prostatectomy patients confirmed the prognostic importance of these variables in our trial. I will now show you data from this specific subset of patients that confirms a benefit for Casodex in reducing the risk of objective progression.

This slide illustrates the Kaplan-Meier time to progression curve in pathologically staged locally advanced prostate cancer patients at high risk for disease progression defined as a pre-treatment PSA greater than 10, or a detectable post-prostatectomy PSA, or a Gleason sum greater or equal to 7. The Casodex patients are shown, once again, in the orange line. Overall in this high-risk group of patients, Casodex reduced the risk of objective progression, that clinically relevant endpoint in patients with this disease, by 47 percent, a highly statistically significant benefit.

In reviewing the patient populations who are candidates for this treatment strategy, while

again we don?t see an indication for localized disease, we do see a clear treatment effect for high-risk patients who are treated initially with curative intent with either radiation or radical prostatectomy.

Let?s now transition to this other subset of patients. Let?s talk about the use of Casodex as immediate therapy as an alternative strategy. These are patients who are not considered candidates for therapy with curative intent. These are the so-called watchful waiting patients.

Dr. Kennealey, in his presentation, has highlighted some of the controversies regarding the use of Casodex as immediate therapy in patients with locally advanced disease. Given these controversies, the sponsor is not requesting an indication for this subset of patients. However, what I will now show you are data that strongly support a treatment benefit for Casodex given as immediate therapy in patients with locally advanced disease as an alternative to watchful waiting.

This is the Kaplan-Meier curve for time to objective disease progression for Casodex administered

as immediate therapy, rather than watchful waiting. Casodex patients are shown by the orange line. Overall, Casodex reduced the risk of objective disease progression in this subset of patients by 35 percent. This is a clear and highly statistically significant benefit in a subset of patients for which no standard of care exists today.

Now these data come from Trials 24 and 25, so the real question is whether these data can be applied to patients managed by watchful waiting in this country.

Dr. Scher has shown you some of this data. We believe on the basis of similarities between patients managed in the EPC trial program and those being managed by watchful waiting in this country, that there is an absolute relevance of this strategy for the use of this agent.

The similarities between the EPC patients and patients with watchful waiting taken from a spectrum of United States databases show that the groups are comparable in terms of mean age, median PSA, the percentage of patients with pre-treatment

PSAs greater than 4, and the percentage of patients whose Gleason sum is less than 6.

Based upon the similarities of these important biologic factors, we can see that patients in the United States managed by watchful waiting have a similar risk of disease progression compared to those managed in Europe and Scandinavia, and therefore, they will benefit the same as patients in those trials.

Prostate cancer is the same the world over. The last time I checked, prostate cancer doesn't need a passport. Therefore, as we review the patient matrix, the EPC trial program provides data strongly supporting the use of Casodex as immediate therapy in patients with localized disease who are not candidates for therapy of curative intent. This is in addition to the data I showed you that strongly demonstrated a treatment effect in the adjuvant setting for patients with locally advanced, that is, high-risk, disease following therapy of curative intent with either radiation or radical prostatectomy.

As I mentioned to you earlier, the

survival data are simply immature. This is the Kaplan-Meier plot of survival for the EPC Trial Program. Remember, this is a disease, the outcome of which we gauge in terms of 10-year survivals, and today, we are at only a median of 3 years of follow-up. Interestingly, however, that 3 years of follow-up has been sufficient to demonstrate a benefit for objective disease progression.

Now there is one thing that?s important to take away from this slide. You will note that there was no difference between the treatment arms for non-prostate cancer deaths. This observation supports the well-established safety profile of this specific agent.

So in summary, the data from the EPC trial program at a median follow-up of 3 years shows that for the overall trial program, there is a 42 percent reduction in the risk of objective, clinically relevant disease progression. For specific subsets of patients at high risk and in need of therapy, we see a 61 percent reduction in the risk of objective disease progression for high-risk radiation therapy patients,

a 47 percent reduction in the risk of objective disease progression in high-risk patients following radical prostatectomy, and a 35 percent reduction in the risk of progression in patients who would have historically be managed by so-called watchful waiting.

I can tell you that with additional follow-up now out to 4.2 years, the data confirms these same observations, so this trial program has shown a significant treatment effect for a clinically relevant disease endpoint. The treatment benefit was observed for subgroups of patients for which no standard of care currently exists today.

As a clinician, I strongly believe that Casodex 150 milligrams fulfills an unmet and clinically important need. Thank you very much for your attention this morning.

I would now like to turn the podium over to my colleague, Dr. Mark Soloway, who will be presenting data on the safety of Casodex at this dose. Dr. Soloway will also address the relevance of the dataset we have presented today to clinical practice in the United States.

DR. SOLOWAY: Thank you, Bill. That was really an impressive amount of data, and I know not easy to absorb all of it in a limited period of time.

By way of introduction, my name as indicated, Mark Soloway. I?m Professor and Chairman of the Department of Urology at the University of Miami, in Miami, Florida. In addition to my hat as chair, and many of you in this room have a lot of administrative responsibilities, I see about 100 patients a week as a urologic oncologist. Half of them are prostate cancer patients, and I?ve been involved with the Casodex program for a number of years, and have been participating in the Casodex 150 EPC Program, as well.

Today, I want to initially present to you the safety profile related to Casodex 150. I will then emphasize some of the factors involved with quality of life, concentrating on sexual function, on bone mineral density issues that relate to various treatments, particularly forms of androgen deprivation related to prostate cancer. And then I want to address the clinical relevance of this dataset to

individuals, such as myself, medical oncologists, radiation oncologists in the United States, particularly highlighting the favorable benefit-to-risk ratio of this drug.

We have an extensive database related to Casodex 150 which is, as many of your know, or some of you know, marketed already in over 50 countries around the world, and most recently in Canada, as well. So there are, in fact, over 29,000 patients years of use of Casodex at the 150 milligram dose. And in essence, adverse events are generally quite mild and predictable from the pharmacologic action of this compound.

Now in the EPC program which Dr. See went through with you in detail, I think you?ll note that if we look at adverse events here as indicated on this slide, clearly the most common are breast pain and gynecomastia. But also of note, one will see that typical effects that one sees with the current forms that we have available of surgical or medical castration, if we look at asthenia, if we look at impotence, if we look at hot flashes, they?re almost

the same between the Casodex 150 and placebo, so that?s a dramatic difference from what we currently have available for our patients.

Now the next slide shows withdrawal from therapy on the EPC program. And again here we?ll note that the most common reason for withdrawal, in fact, is adverse events from the Casodex 150 group. And in the placebo group, the most common reason is progression from treatment.

On this slide we see the most common adverse events leading to withdrawal, and as I said, and expected from the way Casodex works, it is due to gynecomastia and breast pain. A small number of patients withdrew due to asthenia or abnormal liver function.

It is important to note that the incidence of severe hepatic toxicity was very low indeed. And, in fact, abnormal liver function studies when they recur related to Casodex are usually reversible despite continued therapy. The few patients who did have severe hepatic toxicity or excuse me, hepatic abnormalities, elevated LFTs, were in fact related to

liver metastasis from their prostate cancer.

The incidence of adverse events and adverse events leading to death for patients on Casodex 150 are quite similar, as you see Casodex and placebo. And the events were of the type to be expected from an older population, strokes, heart attacks, COPD risk problems, et cetera. So I think in conclusion, regarding the safety profile of Casodex 150, it is a favorable profile. That?s how I would look at it.

While there are tolerability issues to be considered, there are no serious safety issues with this compound, and they are consistent with the known safety profile of Casodex from the many patients who have gone on previous trials.

The side effects observed are, in fact, well-characterized, they?re predictable, they are generally mild to moderate, and consistent, as I?ve mentioned, with the known pharmacology of this product. The main tolerability issues clearly are gynecomastia and breast tenderness.

Currently, many urologists, radiation

oncologists and medical oncologists use medical or surgical castration in patients with non-metastatic prostate cancer. That is a quantum difference than what we saw 10 or 15 years ago, when most of our patients, in fact, had metastatic disease, and that?s where we used the androgen deprivation. In fact, despite limited clinical trial data, the most common use of LHRH analogs in the U.S. today are in patients with non-metastatic prostate cancer; that is, the rising PSA.

Surgical or medical castration, as we know, is associated with a list of adverse effects which significantly alter a patient?s quality of life. And some of these adverse events are seen here, hot flashes often requiring, certainly in my practice, additional treatment, erectile dysfunction or impotence, loss of libido. Important one for men who are vigorous, who have occupations, attorneys, physicians, accountants, et cetera, is their cognitive function. And there is now emerging data that typical forms of androgen deprivation; that is surgical or medical castration alter this not insignificantly.

And something that I think will become more important over time is that with increasing use, duration of androgen deprivation, particularly again referring to the medical or surgical castration that we use, be it orchiectomy or LHRH analog, there?s a progressive loss of bone mineral activity, and thus, osteoporosis. And I think in the future, this is going to be a major problem we?ll have to address.

Well, Casodex 150 is a different type of androgen deprivation. It is a potent anti-androgen with a once-daily pill, and I think this is important, one, for compliance having a once a day pill, but also because it frees the patient?s schedule from having to go to the physician every three or four months for that injection. It puts them a little bit more in control. Since testosterone is maintained, there?s a different side effect profile. And, in fact, sexual function and aspects of bone mineral density are, in fact, retained with Casodex.

Now really quite forward looking, remember when this trial was designed, the Scandinavian group decided for patients who had normal erectile function

going onto the trial that they would use a validated questionnaire, and at regular intervals they would ask the men to fill out this questionnaire. Now we say oh, that?s a natural, but this is several years ago when they did this. And this looked at sexual function and sexual frequency.

And if we look at the data on the next slide, and again, this is one of the largest data sets asking these questions in men with prostate cancer, I think you will note that there?s very little difference between the Casodex 150 and placebo, and this is questions related to sexual function.

Now again, those of you who are familiar with various forms of androgen deprivation which lower testosterone, orchiectomy or LHRH analog, there would be a very dramatic difference here. And the next slide shows in the questions related to sexual frequency, again not much difference between Casodex. It?s a little bit lower, but dramatically different than one would expect if these patients had an LHRH analog, for example.

Next slide. Now there is emerging data,

and this is one analysis, of men who received an orchiectomy, comparing to age-matched patients in the population, and they looked at the number of osteoporotic related fractures. And as you can see, as time goes on, those number of fractures increase on men who have had an orchiectomy. And there are several publications now that corroborate that this is the case. And these, of course, add to additional morbidity for these patients when they occur.

To address this, AstraZeneca performed a prospective randomized study of 103 men who either had Casodex 150 or an LHRH analog, and used the standard test dual emission x-ray absorption to monitor bone mineral density at indicated times. And it?s actually pretty dramatic. If you note that the LHRH analog group in the blue on the bottom, bottom because their bone mineral density diminished over time. And by week 96, there is a 5 percent loss. That?s already in week 96, two years. And the level of minus 5 percent is where you start seeing osteoporotic fractures.

In contrast, the men who took Casodex 150, they?re above the line and retained the bone mineral

integrity. And as I said, when we?re talking about men who, if they elect androgen deprivation for rising PSA, they may be on these ?- they may have orchiectomy or an LHRH analog for many years. And I think in the future this is going to be a major problem.

Well, as a clinician who practices in the U.S., obviously, like many of you, there are clinical scenarios for which I would like the opportunity to discuss, and if I discuss, I would like the opportunity, of course, to prescribe Casodex 150. Now this would include patients who have received radiation therapy, who have had a radical prostatectomy, or who may be electing watchful waiting. And by knowledge, by your knowledge, by the patient?s knowledge, and patients are pretty sharp these days, and you heard some of them earlier today, they are at high risk for recurrence or progression of their disease. And I?m going to give you a couple of examples from my practice, which I hope will bring this home.

This first gentleman is 68 years old. He had his cancer diagnosed, so often common scenario.

His PSA was elevated. It was 12.3. He had a biopsy after the digital exam was noted to be abnormal. He was classified as T3, so it was felt that the tumor was just outside the prostate, probably into the capsule. Gleason Score on the biopsy 4 plus 3, and he elected to have external beam radiation therapy, 3-D conformal therapy, which is a very reasonable alternative for him.

Not surprisingly as many of our patients, he was surfing the net and he pulled up one of the nomograms which are, in fact, patients know them more than I do at times, and he says, you know, Dr. Soloway, my clinical recurrence rate is about 50 percent. And he said, "Gee, I want additional therapy. I?m not happy with that. But on the other hand, I don?t want the side effect profile that I?m aware of with an LHRH analog."

Well, based upon this information we heard today from the large, and I think it?s quite large, EPC Program, we know that Casodex therapy will reduce his risk of progression by 61 percent. I think given this information, I, as a treating physician, would like

the opportunity to discuss this approach with him. And then, of course, discuss it. One would want the opportunity to prescribe Casodex 150. He may or may not elect to have it, but I think that opportunity, particularly with the favorable side effect profile of this agent, should be reasonable and available to the patients.

Now the next case is a more very recent gentleman, 65 years old, recently treated I should say. His PSA was 8. He had a clinical T2 lesion, and I performed a bilateral pelvic lymph node dissection radical prostatectomy, and then as we all do, I sat down with him and reviewed his pathology. And he had a Gleason 7, 4 plus 3, and unfortunately, the tumor extended into the left seminal vesicle.

Now from my database of over 1,100 radical prostatectomies and databases, there are some people in the room that have similar databases, this gentleman has a 50 to 70 percent chance that he will initially have PSA, and then subsequently clinical recurrence. And as we?ve heard today from the large Casodex 150 program, the EPC program, he has a 47

percent less chance that he will progress over time if he receives Casodex 150. And I think it is very important to provide the information. The information is out there, and thus, allow the opportunity, if he chooses, to have that agent.

The next patient is a little bit different scenario, and each case, of course, is somewhat different. And I think this again highlights some of the important variables that we have to deal with. This is a 77 year old, very well known. He wouldn?t probably be known to many of you, talk show host. And he deals with important personalities every day.

Well, he found out his PSA was 17. He had a biopsy and he has prostate cancer. Now cognitive function is critical to this guy?s very livelihood, and what he does every day. And parenthetically, he also has a relatively young wife. Again, unfortunately, and not without much discussion, he was said you need an LHRH analog. He was put on this, and he was devastated.

Most importantly, his cognitive function within a couple of months really was dramatically

altered, and this bothered him tremendously. He was almost clinically depressed. In his social life, his reaction with his wife, also was altered. But on the other hand, he was smart enough to know that he wanted treatment. His PSA was 17, and thus the dilemma. And think Casodex 150 would be an excellent alternative for this agent, again because of the possibility to retain some of the functions that one would not have if his testosterone, as experienced already by this gentleman, went to very low levels, castrate levels. Next slide.

Therefore, in clinical practice in the United States, Casodex I think is a good alternative to watchful waiting, providing an option for those patients who want that option. It is also a treatment option I think for men with high risk locally advanced prostate cancer who have radiation therapy, or radical prostatectomy.

From the data that you've heard today, and the adverse events safety profile data, I would conclude that the benefit risk ratio for Casodex is clearly favorable in patients who are at high risk for

recurrence or progression. And most of us, as oncologists, know who these people are, and increasingly the patients know who they are. Right now there?s only one systemic treatment option for them, and that is surgical or medical castration. And many men simply do not want to tolerate the side effects related to that, and that?s why they often choose, whether they have radiation or surgery, much of it is based on the side effect profile.

Indeed, although gynecomastia and breast pain can be an issue in some patients, there are ongoing approaches to management of this problem. Casodex, over all, has a very well defined clinical benefit and risks with proven efficacy, and a well tolerated safety profile. And this has been demonstrated in the largest prospective randomized trial ever performed in men with prostate cancer.

I think Casodex 150 does represent an important treatment option for the patients we treat on a daily basis in the United States, and it fulfills an unmet need. Thanks for your attention, and we?ll go back to Dr. Kennealey.

DR. KENNEALEY: Thank you, Mark.

You?ve seen an awful lot of data today, both efficacy data and safety data, and I would like just to summarize, show the slide again, because I think this slide gets to the heart of what we?re here to talk about today.

Casodex clearly has reduced the risk of disease progression at a median follow-up of three years. The overall reduction was 42 percent. For the subgroups for which we are seeking approval, we have shown a 61 percent reduction in risk in radiotherapy patients, a 47 percent reduction in risk for radical prostatectomy patients, and a 35 percent reduction in risk in localized watchful waiting patients.

This benefit persists at a follow-up of 4.2 years, and these data have led to the approval of Casodex 150 milligrams as an option for men with early prostate cancer in over 40 countries, including Canada just this last month.

Dr. Hoberman has recently sent to all of you a statistical addendum looking at the Early Prostate Cancer Program, and there?s some clear

agreement between AstraZeneca and the FDA on a number of these issues. And I?ve put these areas of agreement on this slide. And they are, Casodex 150 milligrams reduces the risk of progression regardless of primary treatment. Dr. Hoberman has confirmed that patients in Trial 23 are at low risk for progression, and that PSA and stage are important determinants of outcome. He has also noted that objective progression may be suppressed in Trial 23 due to U.S. clinical practice. And he also noted that the central re-read of the bone scans supported the protocolled primary endpoint.

At this point, I would like to digress briefly into an area for which there is some difference of opinion between AstraZeneca and the United States FDA, and that is concerning Trials 306 and 307 that are mentioned quite extensively in the FDA Briefing Document.

I?m going to ask my colleague, Dr. George Blackledge, who many of you remember from September. Dr. Blackledge is the Global Vice President of Oncology, and has been heavily involved in Trials 306

and 307, to give you some information about these trials.

DR. BLACKLEDGE: Thank you, Dr. Kennealey.

I think it?s worthwhile putting Trials 306 and 307 into context. If we look here at the slide based on Dr. Scher?s presentation, we can see the spectrum of prostate cancer from clinically localized disease right through to clinical metastases. As is usual in oncology drug development, we began our development at the more advanced end; namely, in the presence of metastases, and that?s exactly what Trials 306 and 307 began to do.

In metastatic disease, it?s true that we fell short of our objective, and we did not demonstrate equivalence with castration with metastatic disease. We actually had a shortfall which was statistically significant of 42 days in terms of median survival, so we did not feel that we could progress with a metastatic claim at that point. However, as you can see, this trial program also covered clinically locally advanced disease.

And this is the survival curve for Casodex

and castration for local advanced disease. You can see that the two survival curves are basically indistinguishable. We tested this for non-inferiority, and we did not quite achieve non-inferiority. We look for a 95 percent confidence limit for non-inferiority. We only achieved a 91 percent confidence limit for non-inferiority.

Nonetheless, these data and other data from trials carried out in Italy and Spain, strongly suggest that in locally advanced disease, there is no difference between Casodex and any form of surgical or medical castration. But I would say that the overlap is very small between the patient population here, and the patient population in the Early Prostate Cancer Program.

You can see here the differences between the two populations. In Trials 306 and 307, the aim was palliative. In the EPC trial, patients chose not to undergo therapy of curative intent. Castration was considered a standard of care. It had to be for the randomization in Trials 306 and 307. There?s no standard of care for the patients entering the Early

Prostate Cancer Program.

You can see dramatic differences in the median PSA, and indeed, in the T stages, with most of the patients in the Early Prostate Cancer Program having T1 or T2. And these actually not being allowed in Trials 306 and 307. So the amount of overlap that there is between Trials 306 and 307, and the Early Prostate Cancer is vanishingly small. And even in Trials 306 and 307, together with the accumulated body of data, there's a strong suggestion that there is really no difference between Casodex and castration in terms of survival outcome. Over to you, Dr. Kennealey.

DR. KENNEALEY: Thank you, George. And let me now go on to discuss the questions that the FDA has posed, and they're in your Briefing Document. And I have shortened them in order to fit them on the slides.

The first question, in the absence of meaningful survival data or quality of life benefits, are Trials 24 and 25 sufficiently mature to conclude that patients treated with Casodex will derive

clinically significant long-term benefit? And the answer to that question is yes. We have shown the data that Casodex has a clear benefit over placebo with a median follow-up of three years in the overall protocolled analysis, in the individual analysis of Trials 24 and 25, and in the FDA requested analysis.

Additional analysis of these data with now a follow-up of 4.2 years has confirmed this benefit. A substantial delay in disease progression is truly a long-term clinical benefit. We can't lose sight of the fact that delaying progression to bony metastases is meaningful to men with prostate cancer, nor lose sight of the fact that patients with metastatic cancer face a lifetime without prospect of cure.

And the second question, do the lack of valid Gleason Scores allow for the adequate definition of a patient population that can be extrapolated from the non-U.S. studies to define groups of U.S. patients who will benefit from Casodex therapy. Yes, patient clinical benefits from Casodex can be predicted without standardized Gleason Scores.

In the literature, Gleason Score is a less

predictive variable in prostate cancer, and is not a fully independent variable. PSA and disease stage are considered to be better indicators of patient outcome. And the multi-variate analysis that we performed in the Early Prostate Cancer Program showed that Gleason Score was not independently predictive of outcome.

And the third question, what population of patients initially treated with radical prostatectomy or radiation therapy with curative intent in the United States would benefit from adjuvant treatment with Casodex? And this is really an approval question.

Based on the literature that has been published since the close of recruitment in 1998, we have defined the patients who are at highest risk for recurrence following radiotherapy and radical prostatectomy. For radiotherapy patients with locally advanced disease, and a pre-radiation PSA of greater than 4, we have shown a 61 percent reduction in the risk of progression. For radical prostatectomy patients with locally advanced disease, and at least one of the following, detectible post-operative PSA,

pre-op PSA greater than 10, or Gleason Score of 7 to 10, we have shown a 47 percent reduction in the risk of progression.

These patients, as mentioned by Dr. Soloway, are seen in U.S. practice. They progress in U.S. practice, and they need new and effective treatment options. And based on these data, this is the indication we are seeking. Casodex as adjuvant to primary therapy and men with locally advanced disease defined according to the recent urologic literature. And we ask your endorsement for this indication.

And finally, question 4. Has AstraZeneca demonstrated in Trials 24 and 25 that U.S. patients with localized non-metastatic prostate cancer who are presently managed by watchful waiting would derive sufficient benefit from Casodex to justify the associated adverse events. This is actually the second approval question.

The data that we have shown support the benefit of Casodex as immediate therapy in men with localized prostate cancer. The risk of progression was reduced by 35 percent. We have demonstrated the

relevance to U.S. practice for nearly 20 percent of patients are currently treated expectantly. We have shown that these patients are at significant risk for progression, and that U.S. patients are well represented in Trials 24 and 25.

The longer follow-up data do support these findings, and the benefit of delaying risk to metastatic disease clearly outweigh the side effect profile in this patient population. Thus, we are seeking as an indication Casodex 150 milligrams as immediate treatment of localized non-metastatic prostate cancer for patients who do not receive therapy of curative intent, and we ask your endorsement for this indication.

And my final slide, we have established the basis for approval for Casodex 150 milligrams. We have shown that Casodex delays objective progression in the patient subgroups for whom we are seeking endorsement. The patients who will benefit are well characterized in the presentations you have just heard. Casodex preserves sexual function, sexual activity and bone mineral density. The safety profile

is favorable for the intended population, and Casodex fulfills an unmet need, and provides an important treatment option for patients with prostate cancer. Thank you.

CHAIRPERSON PRZEPIORKA: Thank you, Dr. Kennealey. And at this time, I?d like to ask if Dr. Schoenberg could come forward and take his seat, because I think we want to have the Committee ask the sponsor questions at this point. And I will actually open that question asking period with questions for Dr. Kennealey or Dr. See.

Specifically, you have asked for approval for two specific indications, and the data that I have seen demonstrates significance for these two indication when data from three trials are pooled together. And in a data fishing and data mining type of analysis, I always get concerned that we may lose our reproducibility, or that a negative in one study will be covered by a positive in another. So your first request is for immediate treatment of patients with localized disease, watchful waiting. In Trial 24 and 25, that subgroup in particular are the endpoints

positive in each trial separately?

DR. KENNEALEY: The question is, are the ends for localized disease in the watchful waiting patient group positive separately? And I'll ask Dr. Charles Morris, who is the Senior Director of Oncology for AstraZeneca to respond to that question.

DR. MORRIS: Charles Morris, AstraZeneca. Yes, the treatment effect as we've seen for the localized watchful waiting group overall is reproduced within Trials 24 and 25, as you can see on this slide, with the 32 percent reduction in Trial 24, and 39 percent reduction in Trial 25.

CHAIRPERSON PRZEPIORKA: And in parallel, you've asked for approval for adjuvant treatment for locally advanced disease after radiotherapy or prostatectomy. And are the endpoints significant in Trials 23, 24 and 25 individually for that subgroup of patients?

DR. KENNEALEY: Dr. Morris, do you want to come back and address a similar question with regards to the two other endpoints for which we are seeking approval?

DR. MORRIS: Yes. In your initial comment, you made the comment about fishing expedition. What we actually did, based on the overall treatment effect from the trial program was try to work with FDA to define the benefits in patients more clearly. I apologize.

For the high risk patients on radical prostatectomy, what we see on this particular slide is that the effects are seen within Trials 24 and 25, but less of an effect is seen in Trial 23. This, as has been discussed in Dr. See?s presentation, really seems to be consistent with some of the events which have been going on in terms of U.S. clinical practice, where the number of patients who received additional therapies at PSA progression was actually much higher in the United States trial.

For the radiation therapy patients, which should be appearing on the slide in a moment, there was once again, reproducible effects in both Trial 24 and Trial 25. There were only a very small number of radiation therapy patients meeting these criteria within Trial 23.

CHAIRPERSON PRZEPIORKA: Dr. Martino.

DR. MARTINO: I have two questions. The first relates to the intended length of treatment in patients who did not have some evidence of progression of disease. Do I understand correctly from the slides that in the American trial, the intended length of treatment was two years, but in the European trials it was five. Is that correct?

DR. KENNEALEY: That is correct. Actually, the intended duration of treatment in all three trials was initially two years. And as the two year time point approached, the American principal investigators elected to keep to the two year time frame because this was a true adjuvant trial. And the investigators for the other two trials where a large number of patients were watchful waiting, they elected to change the endpoint.

At that point, we had amassed an enormous safety database, and they felt comfortable extending the duration of treatment as a result of that enormous safety database.

DR. MARTINO: And that may become

important, as you know from your work in breast cancer with Tamoxifen.

DR. KENNEALEY: That?s correct.

DR. MORRIS: The length of time is important, so that?s why I wanted those clarified. The other question that I have is, am I correct that the withdrawal of patients on Casodex is 27 percent? Is that accurate?

DR. KENNEALEY: The withdrawal of patients on Casodex is indeed 27 percent. That is accurate.

DR. MORRIS: Now that, to me, is a striking number. Okay? That means that nearly a quarter to a third of patients choose to come off because of a side effect. Do we know ?- so that?s a problem in and of its own, but the other question that follows that in my mind is, is that number different in the U.S. versus in the non-U.S. studies? In other words, do we have more patients in this country who came off because they perceived toxicity?

DR. KENNEALEY: Okay. I believe Dr. Tom Morris will come up and answer this question. Dr. Morris is the Medical Director for AstraZeneca

Oncology in Europe.

DR. MORRIS: Tom Morris, AstraZeneca.

The large part of that 27 percent withdrawal rate from Casodex is due just to adverse effect, gynecomastia and breast pain, which account for 16 percent. When you take that out of the equation, there is no difference between the Casodex response. If we look across the three trials, we do see some differences in withdrawal rates, that?s true.

The withdrawal rate in Trial 23 is somewhat higher than in Trials 24 and 25, particularly with regard to gynecomastia and breast pain. With regard to other adverse events, there?s very little difference in withdrawal rates.

CHAIRPERSON PRZEPIORKA: Dr. Hanno.

DR. HANNO: I have a question with regard to the bone scans. Bone scans are notoriously non-specific, and even in your re-reads, 27 percent of the ones originally read as positive were thought to be negative, or at least not positive. So how did you confirm the positive bone scan findings indicating that these were true metastatic lesions, since so much

of your application is based on the positive bone scans?

DR. KENNEALEY: I?d like to ask Mr. Kevin Carroll, our Statistician, to respond to the question concerning bone scans and the bone scan re-read that we performed.

MR. CARROLL: Thank you. Kevin Carroll, Statistician. I think it?s important to point out that the bone scan re-read exercise was designed to assess whether there was any bias in the local reading of scans. And in concordance with the review provided by Dr. Hoberman, the re-reads indeed showed no evidence of any bias in the local reading of bone scans between Casodex and placebo treated patients. And, therefore, the time progression endpoint as defined in the trial protocol at the outset, is fully supported by the re-read results. Thank you.

DR. HANNO: My question is though, if in reality half ?- there are studies that show that in cancers where the bone scan turns positive when it?s been negative, only about 14 percent may be true positives, and people do MRIs, they do KUBs, they do

other studies to see if there?s a reason for this. Even if it?s the same in both groups, if the actual number of true positive bone metastatic events is half of what you have in the study, how would that affect your results?

DR. KENNEALEY: Let me ask Dr. Charles Morris to respond to that.

DR. MORRIS: I think we need to point out that the incidence of bone scans was not purely on with the two year, if you like, screening bone scan. The majority of the bone scan events that we have seen occurred when a patient either developed pain, or the patient had a rising PSA, so around about 80 percent of those events are actually based on a clinical indication for the bone scan. So no, we did not perform additional radiographic confirmations, but it did fit into the clinical scenario that we see within prostate cancer.

CHAIRPERSON PRZEPIORKA: Dr. Blayney.

DR. BLAYNEY: I have two questions. One relates to the, if you will, bad things that happen with androgen deprivation, either chemical or surgical

castration. We saw some reassuring data that your compound does not lead to osteoporosis. Dr. Soloway, in his vignette, talked about the cognitive, essentially debilitating cognitive function loss with LHRH agonist. Do you have any data with Casodex to be reassuring in that regard?

DR. KENNEALEY: We have not specifically examined cognitive function with regard to Casodex.

DR. BLAYNEY: Secondly, a large measure of your indication hinges on what you call watchful waiting in Europe. And as a medical oncologist in this country, we do get a fair amount. I?d like to get some sense, perhaps from one of your European investigators, what actually happened during your investigation. Were there patient ?- during your clinical trial. Were there patients who were prevalent, if you will, or who were being followed in clinic, and then all of a sudden the next time they appeared their physician said, "Oh, we have this potentially new drug. Would you like to be involved?" Or was there some triggering event that said, "Now is the time for you, sir, to be involved in this clinical

trial." Because those are, I think, two different iatrogenic stimuli, if you will.

DR. KENNEALEY: I?d like to ask Dr. John Anderson, who is one of the investigators in the European trial, to respond to the treatment practices concerning watchful waiting.

DR. BLAYNEY: And this trial, Dr. Anderson, you were in the European or in the Scandinavian?

DR. ANDERSON: John Anderson. I?m a urologist from the U.K. I was involved in Trial 24. The scenario you described is exactly the case. We have a number of patients who elect to go on watchful waiting in the U.K. They are more concerned about the potential morbidity that goes with radical prostatectomy, or radical radiotherapy, and elect to sit on a watchful waiting program.

Nonetheless, these men remain concerned, and obviously when they come to clinic, the first thing we do is check their PSA, and we can?t get away from the rising PSA story. The patient?s disease may not have changed, but he starts to see something

alter. Along comes a trial where we're exploring a new agent, and we offer the patient to be randomized into this trial to see if it's going to make a difference for him. I'm a great believer in sharing that information with patients explaining the limitations of the treatment, but also illustrating the potential benefits, and many patients with a rising PSA on a watchful waiting program were keen to be enrolled in this study.

DR. BLAYNEY: So I'm given to understand that the stimulus to enroll in this study was some action perceived on the part of the patient, not a new trial opening in your or other centers.

DR. ANDERSON: Not at all. It was a shared concern between clinician and patient.

DR. KENNEALEY: Let me ask Dr. Peter Iverson, who was the principal investigator of the Scandinavian trial to respond to your question, as well.

DR. IVERSEN: With regard to your questions about whether some of these patients were prevalent patients, I can inform you that in the

Scandinavian trial, actually most of them were newly diagnosed patients, the median time from diagnosis to enrollment in the trial was three months.

DR. BLAYNEY: Was three months, you say?

DR. IVERSEN: Three months.

DR. BLAYNEY: Thank you.

CHAIRPERSON PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: There's been a considerable discussion about the Gleason Score, so I have a technical question, and then a question about some of your conclusion slides. Was there a central pathology review of the European pathology slides to address the issue of Gleason stage, or was this determined by the local pathologist?

DR. KENNEALEY: This was determined by the local pathologist.

DR. KELSEN: Is there any particular reason that you elected not to have a central pathology review?

DR. KENNEALEY: Let me ask Dr. Charles Morris to respond to our reasons in deciding against central pathology review.

DR. MORRIS: You remember that the primary intent of the trial was to demonstrate an effect overall in patients with early prostate cancer, irrespective of radical prostatectomy, radiation therapy, or watchful waiting. There was no specific requirement or entry criteria based on Gleason Sum, nor was there any a priori intent to analyze results in terms of ?- in relation to Gleason Sum, so we did not see a need prospectively to define a central pathology review.

DR. KELSEN: So if I just follow that up, in CC-7, in your conclusion slide to partly address this, you made the point that Gleason was not an independent variable, and was not an important part of making a decision regarding treatment, so I?m curious how on CC-9, one of your requests for patients who derive greatest benefit is radical prostatectomy patients who have locally advanced disease and any one of several criteria. And as I read this, maybe I?m reading it wrong, it?s one or the other.

DR. KENNEALEY: One or the other, in addition to having locally advanced disease.

DR. KELSEN: Right.

DR. KENNEALEY: That?s correct.

DR. KELSEN: And one of those is a Gleason Sum of 7 to 10.

DR. KENNEALEY: Yes, that?s correct.

DR. KELSEN: So it?s not an independent variable, but it can be chosen to choose a patient population.

DR. KENNEALEY: Absolutely. We clearly believe that a Gleason Score is important and continues to be used by clinicians and pathologists, but in our review of the literature, and in a review of our own database, it came out to be less predictive than tumor stage and PSA.

CHAIRPERSON PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: A couple of questions. First off, if AstraZeneca can start bringing up CE-37 while I ask both AstraZeneca and the FDA, is there any drug in LHRH agonist perhaps that is currently approved for these indications for adjuvant therapy?

DR. KENNEALEY: You?re asking for CE ?-

DR. BRAWLEY: 37.

DR. KENNEALEY: 37. These are the three indications ?- is that the slide?

DR. BRAWLEY: The first question is about the LHRH agonist. Are they approved for ?- it?s my impression that there is currently not any drug approved for these indications. AstraZeneca ?-

DR. KENNEALEY: Dr. Charles Morris will respond to that.

DR. MORRIS: In the indications we are seeking, there are currently no specific indications in the adjuvant setting. There is neo-adjuvant indication for radiation therapy patients, LHRH agonist, combined androgen blocking.

DR. BRAWLEY: Okay. One of the things that I frequently worry about is truth in advertising, and whenever I want to argue something, I usually use relative risk. And whenever I want to argue against something, I usually use absolute risk. Let?s look at 42 percent there overall, and please tell me if I?m wrong. I believe that refers to slide CE-13, and if we can go to CE-13.

DR. KENNEALEY: It?s the reduction, the

relative reduction in risk.

DR. BRAWLEY: Yeah. Now the way I read that, and perhaps you statisticians can correct me, is if we treat 100 men with Casodex for five years, 4.8 will benefit. Is that correct?

DR. KENNEALEY: I?ll ask our statistician, Mr. Carroll, to respond to that. But I?d also preface his remarks by mentioning that this reduction in relative risk is in line with or actually exceeds the reduction in relative risk seen with Tamoxifen ?-

DR. BRAWLEY: But that?s for mortality.

DR. KENNEALEY: ?- in the breast cancer studies. Both for time to objective progression and for mortality.

DR. BRAWLEY: Yeah. But see, my problem ?- I?ll already play my hand. My problem is, Tamoxifen has been shown to reduce mortality at these rates, and you?re showing that there?s a reduction in disease recurrence at these rates. There?s a difference between recurrence and death.

DR. KENNEALEY: Clearly, reduction in objective progression is important because it means

the delay in development of metastatic disease.

DR. BRAWLEY: Okay. I?d much rather see you in your insert if you did this indication, not say there?s a 42 percent reduction, but say that 5 percent of the guys getting this drug benefit.

DR. KENNEALEY: Let me ask Dr. Scott, Head of Regulatory Affairs, and one of our statisticians to respond to that.

DR. SCOTT: Mark Scott, AstraZeneca. You?re correct that the reduction in risk for Tamoxifen, there was a survival benefit, but the original approvals for Tamoxifen were based on a reduction risk of time to progression.

DR. BRAWLEY: All right. Can we go to CE-26 now? Now there you said there was a 61 percent reduction. By my calculations that means if you treat 100 men, 15.6 benefit at five years, or at four years. Excuse me. Is that correct?

DR. KENNEALEY: That is correct, but let me ask Dr. Blackledge to amplify on the data on the slide.

DR. BLACKLEDGE: George Blackledge,

AstraZeneca. I think we have to be quite careful about making absolute differences, because this is actually summing the data for the whole population. And actually, you could have an effect for every single patient, a smaller effect for every single patient actually making this up, so we cannot talk in terms of having to treat a hundred patients to benefit 27 or 13, or whatever it is. You can actually be getting the benefit, as we believe we do in breast cancer in the adjuvant setting, across the whole population, so I think it?s probably inadvisable to be talking about treating so many people to get so much benefit, because you can actually be benefitting the whole target population to a greater or lesser extent.

DR. BRAWLEY: Then I?d actually prefer to see median days increase disease free survival as the way that you present the data. But again, bear with me again. CE-29, by my way of presenting the data, instead of a 47 percent decrease in risk, 6 percent of men who were treated with this drug actually end up benefitting at four years. That?s how I actually would prefer to think of it, and on CE-33, instead of a 35

percent decrease in risk, I?d prefer to say that 5 percent of men treated over four years benefit. And I think that by doing my 5 percent in the percent, I?m actually statistically averaging over the population where I?m talking to one individual man, very much in the same way you were talking, Dr. Blackledge. Thank you.

CHAIRPERSON PRZEPIORKA: Dr. Carpenter.

DR. CARPENTER: I want to disagree pretty strongly with that interpretation of the data. These absolute risks are on the order of magnitude absolute which you?ve seen with Tamoxifen, you get a much more informative effect of the therapy by looking at a difference in the medians as you suggested. If you discuss it with patients, you also get very different reactions, and this has been done both ways.

It?s likely that you get a benefit across most patients, and the ?- if you analyze the curves the other way, you probably do get a sum of benefit. If you look at your progression free survival median differences, which are not presented here but which actually be quite ?- you couldn?t use medians but you

have to cut it perhaps the 75th percentile because it?s early. You?d see very dramatic differences which have spread through the population. And the vertical difference greatly under-estimates the population benefit.

DR. BRAWLEY: Perhaps I didn?t say it clearly. I wish they had presented the data by progression free. I?m wondering why it wasn?t. And I still have a very open mind as to whether this should be favorably moved upon or not, but I wonder one, why not the progression free analysis. And two, why spend so much time talking about the relative risk and not talking about absolute?

DR. CARPENTER: Well, the absolute risk is on the same order of magnitude as I?ve seen with treatment of node negative pre-menopausal breast cancer, which this situation has a lot of ?-

DR. BRAWLEY: For survival, not for recurrence. Correct? Now if this were survival, if these numbers were in survival, I?d say this is a slam dunk. This is easy.

DR. CARPENTER: Yes. It?s too early to

present this for survival. In general, the survival benefit has been in breast cancer about half that. The absolute differences seen in recurrence fairly consistently across the board in the overview. We don?t know if that?s what?s going to happen in this population because there?s not any long experience to make a judgment on that. But the ?- even the magnitude of reduction in the lapses on this order of magnitude in young women with node negative breast cancer.

CHAIRPERSON PRZEPIORKA: And just to add here, if you want to talk about the breast cancer patients, many of them will say no to Tamoxifen adjuvant therapy when they know that the absolute risk is very small, and the incidence of side effects is larger than their absolute risk of relapse. And with a 25 percent withdrawal rate because of toxicity from this drug, I think Dr. Brawley makes a good point. Dr. George.

DR. GEORGE: I wasn?t going to comment on that, but since Dr. Brawley brought it up, I?ll mention it. Both are correct ways to look at things. It is a difference in emphasis. The relative risk is an

average over time in these time to event things, but may translate into a very small absolute risk at the end of the day. But I have a couple of questions.

One is, I can?t help asking since I haven?t ?- we?ve heard a good explanation of how these studies differed with respect to the patient populations. I had a question as to why, not that it might affect the decision today, but it?s just ?- it?s a question left hanging for me. Why were the studies designed this way? Why didn?t you try to get more comparability among the studies, watchful waiting patients from the U.S., lower risk patients from the other countries. Is there some explanation for this?

DR. KENNEALEY: Sure. Let me start by answering the final part of the question first. The U.S. trial was actually designed as a true adjuvant study, and therefore, watchful waiting patients were not entered into the U.S. trial. And the overall objective of the trial program was to get patients over the entire continuum of prostate cancer, and that?s why there were different entry criteria over the three trials.

DR. GEORGE: Yeah, but am I missing something here? Wouldn?t it have been nice to have ?- at this point to have had watchful waiting patients from the U.S. on this study to sort of add to the evidence?

DR. KENNEALEY: It would take one question off the list, certainly. But we did set it up, indeed, in 1995 as an adjuvant. That was a question that was thought to be very important for the U.S. investigators.

DR. GEORGE: All right. I don?t want to beat that. It was just something bothering me.

Now the other question has to do with something I?m concerned about, is the follow-up information, the length of follow-up.

DR. KENNEALEY: Yes.

DR. GEORGE: One sub-part of that is the ?- you mentioned it was a meeting of three years, I think, follow-up.

DR. KENNEALEY: Yes.

DR. GEORGE: And then you said that everything remains the same at 4.2 years, but have we

seen that data, or is that just what you?re saying?

DR. KENNEALEY: The data ?- the three year median follow-up data was part of the original submission. The four month safety update was submitted to the FDA more recently than the submission, and that included data up to 4.2 years for safety. At the request of regulatory agencies outside the United States, we?ve looked at that data, and the efficacy data have not changed.

DR. GEORGE: And the ?- but we?re just taking your word for it, I mean.

DR. KENNEALEY: We'd be happy to show you that data if you wish.

DR. GEORGE: Okay. And the data presented, if I?m looking at it right, overall, if you just take all the studies together, about 11 percent of the patients have progressed, and the primary endpoint is time to progression. I?m just adding up all the studies. And it?s strikingly different, of course, by study. In the U.S. only about 5 percent. And this is over a time frame that I would just guess, although it wasn?t presented, what the median time to

progression, again over all the studies, would probably be something on the order of 7 years, sort of a median time. So all those things put together, I mean, this is pretty early. Even though you?ve got some strong differences in the 24 and 25 study, this is early in this ?-

DR. KENNEALEY: This slide shows the progression of events over the entire clinical program at the 4.2 year median follow-up, and we?re now up to about 17 percent progression rate. Again, the hazard ratio and the statistical significance is really substantial. At the three year median follow-up, there were 14 zeroes after the decimal point. There?s a few less now, but I mean, it?s still very statistically significant. And despite the fact that there are less than 20 percent progression events, it?s our belief that these data are unlikely to change.

DR. GEORGE: And you will ?- you are still following the patients.

DR. KENNEALEY: All patients continue to be followed for progression and survival in this trial, but again, the data are so compelling at this

point from a statistical and clinical standpoint, that we believe they?re unlikely to change.

CHAIRPERSON PRZEPIORKA: Dr. Shames, did you have something to clarify?

DR. SHAMES: Yes. WE have now reviewed the 4.2 year data that was not in the supplement we?re talking about today at all. It was the earlier data. We actually, just to explain what happened, we offered the sponsor the option to resubmit this with the later data, and they elected to go this route instead, so we have not reviewed that data. And actually, it?s other information I see this morning that we have not had a chance to review.

DR. KENNEALEY: Yes. And that is why those data were not in the primary presentation. The four month safety update, however, has been submitted to the agency.

CHAIRPERSON PRZEPIORKA: Dr. Albertsen.

DR. ALBERTSEN: In Trial 23, you mentioned that the initiation of anti-androgen therapy has confounded the likelihood that a patient would reach one of the primary endpoints. Could you tell me

exactly how patients in each arm of Trial 23 were withdrawn because of this condition, and what criteria were used to have them start on anti-androgen therapy?

DR. KENNEALEY: Okay. I?m sorry. I didn?t hear the final portion of your question. What criteria were used for ?-

DR. ALBERTSEN: In other words, what made the patient drop out? Was it patient volunteerism? Was there a criteria they had to have a rise in a PSA, or was it just the patients who chose to drop out because they thought their PSA was rising?

DR. KENNEALEY: So the question is criteria for withdrawal. I have to apologize. I am directly under the blower so it?s sometimes difficult for me to hear, so if I ask to repeat the question, that?s why.

DR. ALBERTSEN: The criteria, and the absolute number of patients in each arm.

DR. KENNEALEY: Okay. I?ll ask Dr. Charles Morris to respond to that.

DR. MORRIS: The number of patients who had additional therapies introduced within Trial 23

was 10 percent on the ?- or 9.5 percent on the placebo arm, and 7 percent on the Casodex arm. The information that we have suggests that that was in response to a rise in their PSA. The intent of the trial, as you know, was to follow until clinical objective progression.

DR. ALBERTSEN: So that?s 9.5 percent of 1,000, are you telling me, of the 1,645, or ?-

DR. MORRIS: Yeah. Approximately 1,600 patients. Yes.

DR. ALBERTSEN: So you?re telling me roughly 164 patients were withdrawn from the placebo arm, and slightly less from the Casodex arm because of a potential rise in the PSA, or some other explanation that would justify additional therapy.

DR. MORRIS: That?s correct.

DR. ALBERTSEN: Thank you.

CHAIRPERSON PRZEPIORKA: Dr. Krist.

DR. KRIST: One of the things that I?m interested in is the generalizability of studies 24 and 25 to the U.S. And I?m interested somewhat from the other end. I?m a family physician, and we?re part

of a practice-based research network. And within our group, most of our 50 to 70 year old patients, about 70 percent of them opt to get screened for prostate cancer.

DR. KENNEALEY: Sure.

DR. KRIST: And when looking at the characteristics of the patients with prostate cancer in Trial 24 and 25 versus 23, 24 and 25 look more advanced. I?m interested in what some of the screening and diagnosis practices are in the countries for 24 and 25, and how that differs from the U.S. And then what component of how ?- what?s been presented here is that Trial 23 was designed to look at earlier prostate cancer, but I?m interested in what component of Trial 23 showing earlier prostate cancer is more a reflection of different practices in different countries.

DR. KENNEALEY: Let me start by asking Dr. Anderson to respond to screening practices in the United Kingdom.

DR. ANDERSON: Thank you very much. There are clearly Transatlantic differences in terms of

early detection for prostate cancer. Whilst there are well-established recommendations for screening in the U.S.A. from the American Cancer Society, I understand, the American Urological Association, in the U.K. that is not the case. It was only very, very recently that the National Cancer Plan was instituted. It?s now advised that patients over the age of 50 can ask their family practitioner to have their PSA checked. The family practitioner is instructed not to raise the subject with the patient if he doesn?t.

DR. KENNEALEY: Dr. Iversen, do you want to expand on what happens in Scandinavia?

DR. IVERSEN: Yeah. With regard to the part of your question addressing whether there?s a difference in the way the disease appears across the Atlantic, I would say that there?s absolutely no evidence of a Transatlantic difference in tumor biology. An aggressive PSA-based detection strategy in the U.S., combined with a long natural history of the disease has introduced a lead time with more small tumors being detected in this country. However, the more than 30,000 American patients dying from the

disease, and the more patients suffering from the morbidity, pass through exactly the same stages and phases of the disease as European patients do. And it is my belief that these patients, as their European counterparts needs and deserves all the best treatment options possible.

DR. KENNEALEY: Thank you. Does that answer your question?

DR. KRIST: Well, it does. And certainly there is a component of a lead time bias. There?s also probably a component though of a prognostic bias if you?re having higher screening than that.

DR. IVERSEN: Yes.

DR. KRIST: You?re going to find more clinically insignificant cancers. Once again, I?m interested some if the difference in the tumor characteristics between 24 and 25 versus 23, was more relation to the inclusion/exclusion criteria.

DR. KENNEALEY: Okay. Sure. I?m going to ask Dr. See to come up to the podium in just a moment. I think what we need to explain more fully is the difference in the patient population who are

candidates for Trial 23, and the totality of patients with prostate cancer who are treated surgically or with radiation therapy in the United States. It?s actually a bigger group, and that matches 24 and 25 quite well. Let me ask Dr. See to expand on his practice.

DR. SEE: I think that the differences that we?ve observed in the risk profile, if you will, across the overall clinical trial program are driven by enrollment criteria. But in fact, those enrollment criteria were intended to capitalize upon differences, if you will, that existed in 1995 across the different nations participating in this clinical trial program.

CHAIRPERSON PRZEPIORKA: Dr. Martino.

DR. MARTINO: In the three studies, was there a frequency at which the PSA was to be measured, and was that frequency constant throughout the three trials? Question number one. And if, in fact, they were measured, was there some behavior that was recommended in the protocols as to what was to be done when the PSA would rise?

DR. SEE: Okay. The PSA was measured in

all three trials every three months, and we looked at the differences among ?- we looked at each of the three trials to see if there was a difference in frequency that might create some bias, and there was neither a difference in frequency across the trials, or between the arms in the trial. And there was no recommendation from the protocol as to what action to take upon the finding ?- upon the results of the PSA measurement. A PSA rise was not considered to be ?- for the sake of the protocol was not considered to be evidence of objective progression, because the FDA did not and does not recognize that as a valid endpoint.

CHAIRPERSON PRZEPIORKA: Dr. Redman.

DR. REDMAN: A follow-up to some of the points. Specifically, Dr. See?s Slide 18, where there was a difference in the median going to another line of therapy. And the question I have with that is that since survival isn?t a question, what was the difference between the Casodex arms across the trials and on each trial, the Casodex arm going onto an alternative form of therapy, and the patients who were not on the placebo going onto an alternative form of

therapy. What is the median difference in that time in months?

DR. KENNEALEY: So the question you?re asking is the median ?- again, I apologize.

DR. REDMAN: The difference in the medians and months between going onto an alternative therapy on the Casodex arm, going to alternative therapy on the placebo arm.

DR. KENNEALEY: Okay. Let me ask Dr. Charles Morris to answer your question.

DR. MORRIS: As you see from the slide, the median point in time has not actually been reached to this point, so the number of the events and the relative reduction in the risk of the events is demonstrated on this particular slide.

DR. REDMAN: But you have no ?- forget the median then. You have no difference in months? Any idea?

DR. MORRIS: Well, at this point in time, obviously, we haven?t reached a median time to event. No.

DR. REDMAN: Okay. One other follow-up

question. For U.S. in watchful waiting, of the 20 percent or so of patients who go on watchful waiting, is there a sense of how many of those is a physician?s decision based on the fact that definitive therapy would not affect survival, and the patient?s request to do that?

DR. KENNEALEY: Let me ask Dr. David Paulson to respond to that question.

DR. PAULSON: Watchful waiting as it?s practiced clinically among urologists in the United States is largely a patient-driven initiative. It?s a patient-driven initiative based upon their own assessment of the risk of their disease, and also driven by their assessment of a need for lifestyle maintenance.

DR. KENNEALEY: I think that?s one of the important reasons why we are looking to seek an indication in watchful waiting, because there?s a clear difference in the tolerance of Casodex, versus as Dr. Soloway mentioned, what is sometimes used in this setting, which is an LHRH analog.

CHAIRPERSON PRZEPIORKA: Dr. Schoenberg.

DR. SCHOENBERG: Yeah, I think this is a follow-up, actually, to a number of previously asked questions, but I?m curious about the definition of the population in the studies performed of patients who would be candidates for watchful waiting, because I think in contrast to some of the remarks that have been made today, my understanding in U.S. practice is that watchful waiting is offered to a very specific group of individuals. It is, although clearly impacted upon by patient preference, not solely driven by patient decision-making. I wonder if you could illuminate that for me? I have another smaller question after that.

DR. KENNEALEY: Okay. Dr. Paulson I think would be the best to answer that.

DR. PAULSON: Clearly, there are patients who have significant competing risks of death, who would be dissuaded from choosing some form of active therapy because it would be felt that their lifetime ?- their life expectancy from competing risks would not be affected. And we usually use, as you know, the ten year interval before we choose a therapy of curative

intent. Physicians, I think, may very well sway patients one way or the other, but at least in our practice when we discuss watchful waiting, it?s largely a patient-driven decision.

DR. SCHOENBERG: Well, perhaps while Dr. Paulson is still up there, let me just ask this as the meat of the question. My understanding of watchful waiting is, it is a therapy designed for patients for whom we assess the biology of their prostate cancer to not be life threatening. And that it is not a matter simply of trying to avoid some other catastrophic outcome from active therapy, but it is a choice for patients for whom therapy may not be necessary at all. I wonder how that figures into the indication here.

DR. KENNEALEY: I guess I?d have to say we would like to be able to do that, but the practice of medicine has not advanced far enough to say with certainty what the biology of a prostate cancer, what the biological progression of the prostate cancer is going to be based on a single point in time, so it?s not quite as easy to address it that way. We?re simply not quite smart enough. Let me ask Dr. Paulson to

elaborate on that.

DR. PAULSON: There certainly have been a series of risk factors identified which would indicate that the patient is at minimal risk for dying of their disease within a ten year frame. And Dr. Albertsen?s group published some very nice data on that showing that if your PSA ?- I mean, if your Gleason Sum is 6 or less, that your probability of dying of prostate cancer within a ten year span is relatively small.

Unfortunately, I?m not quite sure how many of those patients subsequently went on to have some form of castration-based therapy to extend their life span during that interval.

DR. KENNEALEY: To help answer your question, let me just show you the slide again from patient progression on watchful waiting in the United States. And this is at two years, and at five years, and this is based on PSA. And even in patients with a low PSA, the percentage of patients who do go on to require some form of therapy is substantial. Certainly not zero.

DR. SCHOENBERG: So the final question

actually is a small one related to the Gleason Score discussion. How did you decide based on current understanding of clinical biology to group Gleason 7 with 8, 9, and 10, because clearly, I think at least in U.S. practice, those Gleason Sums are not normally lumped together.

DR. KENNEALEY: Okay. Dr. Paulson will respond to the grouping of Gleason Scores.

DR. PAULSON: As you?ve correctly brought up, Dr. Schoenberg, there is an intermediate grade or an intermediate survival expectation for patients that have Gleason Sum 7 disease. There?s a fair amount of controversy as to whether if it?s Gleason 4-3 or 3-4, depending upon the predominant volume of disease, the relative risk. However, the data in radical prostatectomy series would state that if you have margin positive disease with Gleason Sum 7 as your pathology, you have, I believe it?s about a 50 percent probability of having a PSA failure within five to seven years. And the survival data subsequently with secondary therapies I believe has pushed that to somewhere around 14 to 15 years. But with margin

positive disease, that?s a different risk group than just Gleason 7 that is organ confined, as you know very well from the data at Hopkins.

CHAIRPERSON PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: Yeah. I?m somewhat motivated by the old data via early versus late prostate cancer treatment papers in metastatic disease. Do you plan on continuing to follow these groups to determine the overall survival and mortality rates of people who were treated early with Casodex versus those who had delay therapy because they were randomized to get the placebo?

DR. KENNEALEY: We have information on all patients on first treatment following ?- first treatment for prostate cancer following withdrawal from therapy. We don?t have information on subsequent therapies beyond that, and we will be following all patients for initial progression, initial objective progression and survival.

DR. BRAWLEY: Thank you.

CHAIRPERSON PRZEPIORKA: Dr. Blayney.

DR. BLAYNEY: The analogy has been made to

breast cancer, and also your again stimulus for watch and wait treatment was a rising PSA. In breast cancer, it seems to me the ?-

DR. KENNEALEY: I?m sorry. Go ahead.

DR. BLAYNEY: We heard in Scandinavia that when patients had an event, and often it sounded like rising PSA was what triggered the enrollment in this trial. The analogy would be the rising tumor marker in breast cancer. And to my understanding, rising tumor markers in CA15-3 or 27-29 in breast cancer have not been useful in prolonging survival, when treatment is inaugurated based on a rising tumor marker, so I think your ?- I hope that you?re correct in that there is going to be some clinical benefit and some survival benefit to inaugurating in the watch and wait population treatment with your drug based on a rising PSA. But I think the analogy in breast cancer ?- the analogy to breast cancer remains to be proven.

Secondly, the issue of gynecomastia, which was ?- and breast pain was a big issue for treatment withdrawal. When I was trained many years ago before I had all this gray hair, there was breast radiation

to men who were going on castration as a preventative measure for gynecomastia. And I don?t know if any of your experts have any experience on low dose breast radiation to prevent that.

DR. KENNEALEY: Yeah. Let me ask Dr. John Anderson from the United Kingdom to respond to how he looks at gynecomastia in his practice.

DR. ANDERSON: Thank you very much. I?ve been using Casodex both in the trial setting, and also in my clinical practice in the U.K. for some years. You?re right to raise the issue of gynecomastia, and it?s something we address with the patients early-on. We?ve seen the figures. We?ve seen that it occurs.

In my experience, it?s not a major problem, and we do not see patients withdraw once they know the benefits of treatment. I think the high withdrawal rate we see, the EPC data, reflects unknown efficacy of the drug, but recognized toxicity.

What I see in my clinical practice is a different thing. I see patients who we address up front with gynecomastia is an expected event in someone who?s on Casodex, but it?s manageable, and it

should not cause a problem. If the patient has an issue, then irradiation of the breast tissue before we start treatment is something we would discuss with them. We re-address the issue once they're stabilized on treatment, and withdrawal of treatment is always an option. But what I'm absolutely persuaded by is the benefits that the patient perceives in terms of delaying disease progression far outweighs his concerns about the potential toxicity of the treatment. And I feel, therefore, that in my practice it's very important to have that option to offer the patient, and involve him in the discussion of the relative benefits of delaying disease progression against possible side effects. He should have the option.

DR. BLAYNEY: I agree with the involvement of discussion. Finally, Dr. Kennealey, in your slide CI-10, which was the chronology of development, there's a compound and it may come up later in the morning or earlier afternoon about your dealings with the FDA. Were you meaning to imply that there was a change in the rules or the change in the parameters which you

used, or you were required to use to develop this compound?

DR. KENNEALEY: We were asked by the FDA to look at an alternate endpoint of time to disease progression after the close of recruitment. And we, indeed, did that, and that showed that the results of that were congruent with the results from the primary, the initial endpoint.

DR. BRAWLEY: Can we see those results?

DR. KENNEALEY: You want to see the results of the FDA ?- the endpoint of time to bone scan progression? Yes, let me just bring that up for you. This slide shows the bone scan progression, the endpoint requested by the FDA. As with the primary analysis, there is an overall benefit in favor of Casodex with a reduction of 37 percent. That was seen primarily in Trials 25 and 24, as was ?- you know, this really parallels the primary analysis, and actually confirms that analysis.

CHAIRPERSON PRZEPIORKA: Dr. Hanno.

DR. HANNO: I have a question with regard to indication number two. I know you pick your words

very carefully when you go for an indication, and here the indication is localized non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated. To me, and I think to a lot of urologists, that would mean patients who don?t have a ten year life expectancy, because therapy of curative intent would be indicated in the other people, whether or not they chose to accept it.

My question is, would it be better to change that to not planned, and are you looking for therapy in patients who have locally advanced disease, and that?s why they don?t have therapy of curative intent planned, or they don?t have a life expectancy to warrant it, because those are two very different groups.

DR. KENNEALEY: Sure.

DR. HANNO: And there are standard therapies for the other group.

DR. KENNEALEY: Yes. We?d love to ?- we submitted the original indication last year, and as we reviewed our data and reviewed our plans towards coming here, it became very clear that indicated was

not the right word. And that intended, either by the patient or physician, would be a much more appropriate word in our indication. And that would be something that we would want to change.

CHAIRPERSON PRZEPIORKA: Dr. Martino.

DR. MARTINO: I want to add something to this comparison of breast cancer to prostate cancer, and it?s in reference to the use of tumor markers. There actually is a trial that was reported and done in Europe. It was presented in poster form at it was either ASCO or San Antonio about five years ago. It was a patient population that was being followed by tumor marker, and the tumor marker used was a 15.3.

At the time that the patient had a rising tumor marker, and had no involvement that could be seen by clinical exam or x-ray, so in other words, the tumor marker appeared to be the only sign that something might be going on, the patients were randomized to either observation further or to Tamoxifen. And a survival advantage was seen in the Tamoxifen treated arm. It was a small trial. It was abstract, and with all respects to our European

colleagues it was from Europe, and so I think that it was somewhat ignored. Nevertheless, it does exist in the literature, and may be somewhat of a model to this PSA issue.

CHAIRPERSON PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: Two quick questions. Were there any formal studies, a wonderful presentation looking on side effects and quality of life. But were there any formal studies to look at state of well-being of men on Casodex versus placebo?

DR. KENNEALEY: There were no formal studies that looked at state of well-being in men on Casodex versus placebo. The only quality of life study are studies that were presented by Dr. Soloway.

DR. BRAWLEY: I mean, granted, and I accept that it?s very likely that knowing that your PSA is down improves your quality of well-being. I accept that. The other question is, and again, I?m heavily influenced by Dave Byers? studies that showed that early treatment had no greater effect on survival than later treatment granted in a different group of individuals or different patient population. And it

was 30 years ago with different drugs, but I?m wondering do you have any data on response to LHRH agonists in men who progressed after being on Casodex?

DR. KENNEALEY: Yes. Let me ask Dr. Anderson, who has extensive European experience, to address that.

DR. ANDERSON: I have been using Casodex long enough to see men progress, and standard practice for me would be to institute them on an LHRH analog. Response rate is about a third as measured by PSA response, and I think that?s in keeping with any other first line hormone treatment where the patient escapes hormone control.

I don?t know of any sequential studies to say that one sequence is better than another, but where I draw reassurance is when I look back at the 306-307 data, where patients were either treated with Casodex, or with castration. Now in those studies, both patients progressed in either arm. They were treated with alternative second line treatments, and we know that there are no major survival differences for the two groups, so I?m reassured that there?s no

difference in the biology of the tumor after the patient has been treated with Casodex.

CHAIRPERSON PRZEPIORKA: A follow-up question while you?re standing, sir. Did I understand you to say that when you had patients on Casodex, you would start them on second line salvage therapy on the basis of a PSA, and follow the PSA only?

DR. ANDERSON: I?m sorry. Could you repeat the question? It is noisy here.

CHAIRPERSON PRZEPIORKA: For your patients on Casodex, did I hear you say that you would start them on the LHRH antagonist on the basis of a rising PSA only, and then follow the PSA?

DR. ANDERSON: No, you did not hear me say that. When a patient fails hormone treatment, it?s a full clinical picture. The patient either becomes symptomatic, he has a rapidly rising PSA or has changes perhaps on his bone scan that would indicate treatment. It would just ?- it would not just be on a PSA progression.

CHAIRPERSON PRZEPIORKA: Any other questions from the Committee? Dr. Albertsen.

DR. ALBERTSEN: Just a quick follow-up on Dr. Brawley?s question, again to help me understand some of the British data. In England, on Trial 24 when you started patients on Casodex, and when they failed Casodex, they moved on to anti-androgen therapy, was the length of time of response on anti-androgen therapy equivalent to what might have been perceived had they started initially on anti-androgen therapy and run the whole way? Basically, what I?m trying to get at, was there additional response time by sequencing the drug, rather than starting initially on anti-androgen therapy and just waiting to see what happened?

DR. KENNEALEY: Let me just clarify. You meant after Casodex, you mean LHRH. You didn?t mean anti-androgen therapy?

DR. ALBERTSEN: Right. I meant LHRH. Correct.

DR. KENNEALEY: Okay. Thank you.

DR. ANDERSON: I don?t have any personal data to support that, neither do I know of any studies that would support it either. It?s relatively early to

be able to answer that question confidently, but I do reflect back to the 306-307 data, where those sequences occurred in each arm where there were no differences.

DR. ALBERTSEN: Where I?m coming from is, it would strike me from a clinical perspective that Casodex in this country would probably substitute in many instances for LHRH agonist therapy very early on in the practice. And so what I?m trying to grasp is, are we likely to see an extension of survival which we haven?t seen certainly in Trial 23. And I?m not saying you have data here. What I?m getting at as you?re talking about your clinical practice. Is this ?- because what you?re quoting is the survival on Casodex versus standard castration therapy. There was no survival difference, so what?s striking me is that Casodex becomes a substitute, but doesn?t increase survival. Is that a wrong conclusion?

DR. ANDERSON: Well, I think that?s probably accurate. There?s probably ?- there?s no evidence to suggest one way or the other to my mind.

CHAIRPERSON PRZEPIORKA: Other questions?

Hearing none, what I?d like to do is take a break for 15 minutes, be back here at 10 minutes after 11. Thank you.

(Off the record 10:55:28 - 11:14:04 a.m.)

CHAIRPERSON PRZEPIORKA: Okay. We?ll start with the FDA Presentation. Dr. Daniel Shames.

DR. SHAMES: Good morning. I?m Dan Shames. I?m the Director of the Division of Reproductive and Urologic Drug Products at the FDA. Before I start my remarks, Dr. Hoberman, our statistician, has asked to make a few comments.

DR. HOBERMAN: Thanks, Dr. Shames. In retirement, I thought I could be quiet as a mouse, but unfortunately not. The Sponsor made comments about statements I made in my review, and I just wanted to clarify a couple of them because they were made out of context, and I want to provide the full context for the record. Also, I do want to make it clear that I?m a statistician, I?m not a clinician.

The first statement they made was they concluded from my review that Casodex reduces the risk of progression regardless of primary treatment. That

was true in Europe, but I wish they had made it clear that I don?t think that there?s a shred of evidence data that supports efficacy in the United States.

The second point is that patients in Trial 23 are at low risk for progression. I think that was a consensus that we all had that what they failed to mention was that I did do an analysis which tried to account for the lack of treatment difference in Europe, in the United States, based on the different distributions of prognostic variables. And for reasons unknown to me, was unable to account for that difference. So even though that I understand that in the clinical community, I guess it?s sort of common wisdom that one of the reasons that the response rates were so low in the United States in comparison to Europe was that the course ?- where the patients were in the course of their disease, statistical methods surprisingly couldn?t confirm that, and I was disappointed.

The other thing that they quoted was, ?Objective progression may be surpressed in Trial 23 due to U.S. clinical practice.? I have no business

saying that as a statistician, except as in the context of the review, it was one of a litany of different things that might have accounted for the differences between Europe and the United States. And one of the reasons I mention that is because I was involved in the application of Rilutek, the only treatment on the market for ALS, in which there was evidence of efficacy in Europe, but there wasn?t a shred of evidence of efficacy in combined Canadian and North American trials, so I want to make that clear.

There are a couple of very quick things that I would like to point out also for the record, that I want to emphasize, although I know that Dr. Monroe is going to refer to these. One is that when the sponsor showed the slide about the results of 306 and 307, they combined the results and showed that they didn?t make a confidence interval for equivalence or non-inferiority. But the whole point of that was that the FDA decided that those trials could not be combined because of positive results in one, negative results in the other. And when you put them together, there was a wash, and that?s important to point out.

The only other thing I wanted to point out is that this business about the modeling in order to find a subgroup in which there would be efficacy in a high risk subgroup, that modeling exercise is, in a sense, a reasonable thing to do, but I think you ought to keep in mind that when labeling the drug, it?s a very risky business when you?re talking about what are going to be the cut-offs in the prognostic factors, which have been identified in the model. So it may be that they can find a difference in a subgroup when restricted to certain risk variables like PSA end stage, but how the Gleason Score came up, how the PSA score came up as the boundary for who should be eligible for Casodex 150 is certainly not clear, and those cut points must be due to a degree of data dredging that comes from the model that was used to find the prognostic factors.

Thank you very much for the opportunity for me to correct the record.

DR. SHAMES: Hello. I?d like to first thank the Division of Oncologic Drug Products for the close cooperation and advice we?ve had from them during

the course of our reviews of the various applications for Casodex 150. And I also appreciate ODAC for taking the time to advise us regarding this challenging issue being presented before us today.

I would say that whatever differences any of us have we, I?m sure, all agree that these issues ?- the general issue of prostate cancer and the specific issue before us today is extremely challenging.

The FDA?s presentation will consist of the following. I?m going to discuss background and review issues. Dr. Monroe, who is the medical team leader for this product, will review the clinical trial data, and then I?ll come back and summarize the review issues, and introduce the questions.

As far as background, my background comments will include mention of the importance of the issues before us this morning. We heard some of that. A brief discussion of the critical role staging plays in the treatment of prostate cancer, and a few remarks regarding the relevant history of the development of Casodex 150.

The issues being considered today

regarding the use of pharmacological therapy for non-metastatic prostate cancer impact a large segment of the U.S. prostate cancer population, as we all know. Casodex 150 would be the first approved therapy for non-metastatic prostate cancer. The target population could include hundreds of thousands of patients that would take the drug for years, or perhaps decades.

However, because of the variable nature of cancer of the prostate many patients, including those who remain asymptomatic throughout their lives might be exposed to unnecessary risk.

As you all know, prostate cancer is a disease that can exist along a very wide continuum, from microscopic clinically inapparent, to advanced hormonally insensitive disease. For many elderly men, the disease exists in our bodies for many years until they die of something else. Therefore, the treatment for prostate cancer must take into account the dictum ?primum non nocere?, or first do no harm.

We must be careful not to expose patients with early prostate cancer to unnecessary toxicity without proven benefit. Recent evidence indicates

that the most precise method to predict a patient?s disease stage and, therefore, decide on appropriate therapy, such as surgery, radiotherapy and others are outlined in the trial, which I will mention further.

It should be noted that Gleason Scores, which are based on glandular patterns of tumor under low power magnification is essentially the most accepted method of pathologic grading in the United States, were not used in the non-U.S. trials. Traditional pathologic grading was used in the studies outside the U.S., and the results were extrapolated into Gleason Scores. It was more than ?- really there was no central laboratory. The pathology was translated into Gleason Scores, and someone did make the comment about the translation of 7 versus 7, 8, 9, 10, and we also had that problem.

From my reading of the literature, it appears that the best way to ?- at the moment to define cancer sub-populations are the clinicals, the Gleason Score and the PSA. It is true that they all are independent predictors, but the papers that we read tell us that the three together are the best

predictors, and add the most precision to the staging and prognosis paradigm.

We do need to talk a little about Trials 306 and 307. Casodex 150, as you know, has been previously studied in a population of patients with advanced prostate cancer. The information derived from those studies is important when evaluating the potential use of Casodex for earlier forms of prostate cancer. These were randomized parallel studies in advanced carcinoma starting in 1992. The definitions of the populations are seen on the slides.

There were M0 patients, as defined, and M1 patients who were defined with bone mets. These trials involved Casodex 150 versus castration, medical or surgical castration. The intent of the study was to show survival non-inferiority of Casodex compared to castration, and to show a quality of life advantage of Casodex compared to castration.

The Data Safety Monitoring Board stopped the trials for M1 patients because Casodex compared to castration had decreased survival, and increased progression at the time in both trials independently.

The trials continued after that with M0 patients only, and these are the numbers that were in the two trials, and you see Trial 307 is maybe twice as large, or perhaps even larger than Trial 306.

The data, the information from the M1 patients in Trial 306 and 307 were submitted to our division as supplement 06 of this NDA in February of 2000, and the purpose was to compare a combined analysis, the selected dose of Casodex 150 with medical or surgical castration in terms of survival, time to progression and time to treatment failure, quality of life, and tolerability in patients with untreated locally advanced prostate cancer defined as you see before you. And these are the results of the M0 patients. And these are hazard ratios for mortality.

In the smaller trial, the hazard ratio indicated that Casodex treated patient had reduced mortality compared to the patients treated with castration. However, in the larger trial, which was more than twice the size, the Casodex treated patients experienced increased mortality compared to the

patients treated with castration.

The results from the sponsor?s combined analysis revealed that Casodex failed to meet the pre-specified parameter to declare non-inferiority castration. In other words, demonstrate non-inferiority to castration in terms of survival. Casodex was to be no more than 25 percent worse than castration with respect to survival. However, the combined analysis as previously shown the confidence interval was 36 percent.

As previously mentioned in M1 patients, the Casodex was inferior to castration in terms of survival and progression. In M0 patients, the Casodex trials had disparate results. The data from the larger trial indicated decreased survival and increase progression compared to castration.

Our experience with this particular trial in the various patient groups caused us to have concern. Because of these results, the FDA had concerns about overall mortality being adversely affected in M0 patients possibly, and perhaps even earlier patients, or even the overlap patients, so we

found some additional information that might support our concern.

In recently published large meta analysis of single therapy androgen suppression in men with advanced prostate cancer which was published in April of 2000, the author stated, ?The evidence from eight trials involving 2,700 patients suggests that non-steroidal anti-androgens were associated with a lower overall survival compared to castration. The data from the Casodex trials in the meta analysis, especially

The data from the Casodex trials in the meta analysis, especially since there may be a biologically plausible explanation for the survival disadvantage of Casodex compared to castration in men with advanced prostate cancer.

Those who treat patients with prostate cancer are familiar with the phenomenon of anti-androgen withdrawal syndrome, which is a paradoxical anti-androgen stimulation of prostate cancer, perhaps resulting from prostate cancer receptive gene mutation. I don?t think we?re absolutely sure. A

similar mechanism could be in operation to explain the survival disadvantage of Casodex compared to castration in patients with advanced prostate cancer.

Now, it is true that the Trial 306 and 307 were on more advanced patients, and there was only some overlap. But, quite frankly, we don?t know what long-term treatment of Casodex is going to have ?- the effect is going to have on survival because we?re very early in the process here. And considering the data we have, this is an issue of great concern to us.

I?m going to now tell you what the review issues that Dr. Monroe is going to speak about in just a minute or two. Our efficacy concerns have to do with the fact that the trials are really not long enough to demonstrate enduring efficacy as we have defined them. The Gleason Scores are ?- we consider invalid in Trials 24 and 25, not only for the technical reasons I told you, but also -- as Dr. Monroe will point out -- there were inconsistencies between the clinical stage and outcomes and pathology between the U.S. and the non-U.S. trials.

Also, the data proposed to support

efficacy in the U.S. is based on a retrospective subgroup analysis. As far as safety, there is a very high discontinuation rate from adverse events, a high instance of gynecomastia and breast pain. And as you will learn, for many of these people the gynecomastia is irreversible. There?s also some concern about liver toxicity.

Additional review issues were the issue I just discussed, which is questionable. We?re not sure about long-term survival, even in this patient group. We do not believe it?s been demonstrated that there?s a quality-of-life or sexual advantage clearly demonstrated, especially a quality-of-life advantage regarding Casodex. And the three trials that we are presented are heterogeneous populations with different treatments. And the non-U.S. trials reflect different practice patterns.

In addition, we did find in our review what we felt to be some imprecision regarding the bone scans. Dr. Scott Monroe will now report on the details and data for Trials 23 and 24, which were submitted to support Casodex 150 for non-metastatic

prostate cancer.

DR. MONROE: Hi. I?m Dr. Scott Monroe from the Division of Reproductive and Urologic Drug Products. I was originally going to start by saying "good morning," but we?ve almost reached noontime because of the lengthy -- but I think very important -- discussions that we?ve had prior to this time.

Earlier this morning, the sponsor presented their data and their interpretation of these data that were submitted in support of the two indications for Casodex that you see showing on the screen in front of you. In support of these indications, as you?ve heard, the sponsor conducted three multi-center randomized placebo-controlled clinical trials.

Trial 23, as you know by now, was conducted almost entirely in the U.S., and to a lesser extent in Canada, and neither Trials 24 or 25 enrolled any patients in the U.S. Trial 23 enrolled only patients with prostate cancer who had previously been treated by either a radical prostatectomy or radiotherapy. These patients have been referred to as the adjuvant treatment groups.

Trial 24 and 25 enrolled similar patients, but also enrolled patients that had not undergone any prior treatment. And these have been referred in your background documents, as well as in our presentations today, as the "watchful waiting" group, the "immediate therapy" group or "monotherapy" group, all referring to the same group of patients.

One of the most important characteristics of all patients across all trials was that they were all supposed to be negative as far as bone scans. That?s a very important unifying characteristic that crossed all of the trials. An important difference was that treatment in Trial 23 was limited to two years, while treatment in both Trials 24 and 25 continues. And this also applies to the adjuvant patients in Trials 24 and 25, so you can see there is a difference between these trials. It?s not just whether they?re watchful waiting or not, but a decision was made in one adjuvant group treatment would be discontinued, while in the other two trials which also have adjuvant therapies, treatment is ongoing.

Since the sponsor has reviewed the overall

design of these clinical trials, their similarities and differences, and the overall efficacy and safety findings, I will avoid re-reviewing these topics. Rather, I?ll try to limit my presentation to significant clinical review issues. And these review issues include differences between the sponsor and the division regarding study endpoints and data analyses, and interpretation of clinical findings.

I will also review findings of concern to the division. Now, not having had the benefit of knowing exactly what the sponsor was going to present, I will, however, have some duplication, but hopefully we can go over those areas quickly.

Early in the review process, we noted an inconsistency between the Gleason Grades or Scores in the clinical stage of tumor stage and pre-treatment PSA values across the trials. Note that in Trial 23, the U.S. trial, there is a much higher proportion of patients that were characterized as having poorly differentiated tumors, and whether or not this was based on a proper Gleason Score or not, there is a difference, at least in terms of how the pathology or

the histopathology of these tumors was assessed.

You could say almost half the patients in the U.S. were considered to have poorly differentiated tumors, where only a quarter and just a little bit over 10 percent were classified as having similar tumors in the non-U.S. trials. However, if you look at the clinical stage, you can see that patients enrolled in the U.S. had least advanced disease. They had the smallest percentage of patients in Clinical Stages 3 and 4, and we had the highest percentages or higher percentages in both of the two European trials.

This discordance is also apparent when we look at tumor differentiation and pre-treatment PSA values. And once again, we can see -- looking at median PSA values at the bottom of that slide -- they?re lowest in the U.S., highest in the non-U.S. studies, and this is going exactly the opposite than what was determined to be the histopathology of these tumors.

There is also a discordance between the baseline histopathology or Gleason Scores and disease progression. On this slide, we?ve listed for you, for

each of the trials, the percentages of patients in the prostatectomy group who had Gleason or tumors reported as poorly differentiated, or Gleason Scores of 7 or greater. And whether we?re talking about 7s or 8s, I don?t want to belabor that point. We have to go with the data as it was presented to us by the sponsor. But I think the important point I?m trying to make here is that there is less tumor dedifferentiation, at least as assessed by the pathologists in the various trials in the non-U.S. studies; namely, those were better differentiated tumors, yet we can see that the incidence of disease progression as assessed by a positive bone scan was much higher in the non-U.S. trials. And this certainly was problematic for us in terms of interpretation of the baseline disease characteristics of these patients.

Similar data was observed when we look at the subgroup of patients treated by radiotherapy across the three trials. Once again, we see that the percentage of patients with high Gleason Scores or poorly differentiated tumors is highest in Trial 23. Yet, it is these patients that have the lowest or the

least disease progression as assessed by positive bone scans.

Although the sponsor and the division met on many occasions throughout the development of this program, both prior to its onset, as well as while the studies were ongoing, the sponsor and the division never fully reached closure on what the primary study endpoints and analyses should be.

We discussed this somewhat earlier this morning. I?d like to expand on that just a little bit here. The sponsor preferred a time-to-disease progression endpoint, where progressive events were based either on local or distant events of disease progression confirmed by bone scan, x-ray, CT, MRI, ultrasonography, or biopsy, or death due to any cause in absence of progression.

The FDA, on the other hand, preferred an analysis and endpoints based on the proportion of patients with progression within two years post-randomization, where events of progression would be limited to positive bone scans, or death due to any cause in the absence of disease progression.

The rationale for the FDA?s preferred endpoints and analysis was based on concern acknowledged by the sponsor that blinding could not be maintained because of the anticipated high incidence of gynecomastia and decreases in serum PSA in the Casodex-treated patients. We felt that the inability to maintain blinding could result in significant assessment by us. In addition, specific criteria for local disease progression did not appear to be provided in the study protocols, and there was no central blinded review of events classified as progression, whether they be bone-scan-documented or otherwise. Because all the protocols mandated a bone scan at two years post- randomization, it was believed that this endpoint, along with death, would be least subject to possible assessment bias.

On this slide are listed the results from the three clinical trials in which events and analyses are based on the FDA preferred endpoints; namely, a positive bone scan or death, in this case, actually within two and a half years of randomization. And the time interval was extended from two to two and a half

years to allow for inclusion of the patients whose bone scans would be delayed for a small period of time.

In each of Trials 24 and 25, there was statistical evidence that treatment with Casodex delayed disease progression. In Trial 23, however -- the only trial that enrolled patients in the U.S. -- there was no significant difference between the two treatment groups. And as you saw earlier this morning, the same conclusions regarding the effect of Casodex treatment on disease progression were obtained using the sponsor?s preferred endpoints and analyses.

The sponsor?s original proposed indication for Casodex 150 milligrams was immediate hormonal therapy, or adjuvant therapy to treatment of curative intent, patients with non-metastatic prostate cancer. Such an indication would encompass virtually all patients with non-metastatic prostate cancer, and was not, in our opinion, supported by the submitted data.

Because of the negative outcome of Trial 23, the division also concluded that adjuvant treatment in patients with early disease would be of

little, if any, benefit. The division was also unable to characterize -- based on data in the NDA submission -- the population of patients in the U.S. who would likely benefit from Casodex adjuvant therapy.

The sponsor was asked to identify populations treated by a prostatectomy or radiotherapy in the U.S. who would likely benefit from adjuvant therapy, based on the actual data provided in their submission. In response to this request, the sponsor performed post-talk exploratory analyses that resulted in the first of two changes to the proposed indication.

The first revision to the indication concerned the use of adjuvant therapy. That will be our focus for the moment. Based on these analyses of the indication for adjuvant therapy was limited, as you heard earlier, to patients with locally advanced non-metastatic prostate cancer who have a high risk for disease progression.

This modification of the indication was presumably based on analysis performed by the sponsor on their data set, which showed that patients with

stage three or four disease and a detectible post-prostatectomy PSA value, or a pre-radiation PSA value of greater than 10, were most likely to have disease recurrence.

The data supporting this change for the adjuvant treated patients, based on the FDA preferred endpoints, are shown on this slide. And what we can see here -- and let?s focus primarily on Study 23 -- that by this criteria, there were very few patients in the U.S. who had disease progression, as assessed either by a positive bone scan or death within the two-year period after randomization. As you can see, there are only four in the Casodex group, six in the placebo group, and clearly these were too small to make any conclusions regarding the potential benefit of Casodex in this group.

On this slide we can see similar data for patients who were initially treated by radiation, had a pre-radiation PSA value of 10 or greater. Once again, you can see in the U.S. population, there were very few patients who met this criteria, and the number of events were one in each of the two treatment

groups. Once again, not supporting the benefit of this therapy in U.S. patients. You can see there were numeric advantages for Casodex in the radiotherapy patients in both Trials 24 and 25.

We noted during our review of the sponsor?s background document that the definition of a patient of high risk for disease recurrence appears to have expanded somewhat, and this new expanded definition is listed in the lower portion of the slide. These patients remain those with locally advanced stage T3-4 disease and detectible post-surgical PSA values, but also include pre-surgical PSAs of greater than 10, or a Gleason of 7 or greater. And the criteria for a patient treated by radiation has been loosened somewhat, so that a pre-radiation value of 4 would qualify an individual for being at high risk for recurrence or disease progression.

Earlier today, the sponsor showed you a number of Kaplan-Meier curves based on these definitions. And I want to first bring to your attention that the prostatectomy and radiotherapy labels are reversed on this slide. The data in the

upper half of the slide are from the radiotherapy group, those in the lower portion from the prostatectomy group. And we agree with the Kaplan-Meier curves that you saw earlier, if you accept the sponsor?s endpoints, that in the high risk group of patients as defined -- as I showed you just a moment ago -- there were statistically significant reductions in the proportion of patients who had disease progression.

But throughout our review, our concern has really focused on the findings in Trial 23. And you did see a slide showing a breakdown of these patients, at least for the radical prostatectomy group earlier, and here I show you those data once again. And you can see the benefit of Casodex in that combined analysis that we just previously showed was driven entirely by the results of Trials 24 and 25. And one could ask if it was even appropriate to combine all trials together, but that again is really not the issue.

The issue is that if you apply criteria that sponsor has determined to identify patients at

high risk for disease recurrence, and apply those criteria to the population in the U.S., we just at this point do not see any benefit of Casodex treatment. We see a proportion of patients with progression of 6.8 percent in the Casodex group, and 6.4 in the placebo group.

Now the earlier analyses were based on very small numbers, and their significance is questionable. But here, presumably we have 712 patients that are at high risk for disease progression, yet we don't see any benefit at this stage of Casodex therapy. And this, again, underlies the concern of the division that logic would say you could just transfer these data and information from the European studies to the U.S. studies, but it just hasn't worked out when we apply them, or the sponsor in this case has applied them to the actual data.

I do not have a slide for the radiotherapy patients. The sponsor actually showed one, I believe, earlier where they showed that in Trial 23, using the definition of high risk for recurrence, there were only four events -- I believe -- in the U.S. trial, if

I remember. And if I also remember correctly, of those four events, two occurred in the Casodex group, two in the placebo group. So once again, I?d say there is a problem as to what is happening with the U.S. patients.

Now subsequent to the division?s not approving the NDA for Casodex 150 milligrams, the sponsor revised the proposed indication for the "watchful waiting" or monotherapy group. And in the revised indication, as you?ve heard this morning, the sponsor now recommends that immediate treatment or monotherapy be limited to patients with localized Stage T1/T2 non-metastatic prostate cancer. It?s our understanding that this modification was made because of the concerns of the division that Stage 3 and 4 patients were very similar to those in the previous studies, where there were concerns about survival in the Casodex-treated patients.

Sponsor has also shown or at least told you that the effects of Casodex treatment in these earlier stage patients was statistically significant, and that we do agree with that based on the sponsor?s

endpoints and time-to-event analysis. But if you apply to these patients the endpoints and analyses that the FDA feels are more appropriate because of the concerns about assessment bias, we can see that there are certainly strong trends in support of Casodex, but that the upper bound of the 95 percent confidence limits for the odds ratios for both of the studies extend above one. Whether these will drop down below one or whether they have in your more mature data which you've not seen, we just don't know. But at least on the data that we've had a chance to review, neither of these studies would have crossed the bound that would have met the criteria for statistical significance.

It also was of interest to us that the majority of events that were classified as disease progression were actually deaths in this population, but that of these deaths, only about 10 percent, or perhaps a little under 10 percent, are actually due to prostate cancer.

These are the baseline disease characteristics for the patients in the T1/T2

"watchful waiting" groups in Trials 24 and 25. And at first glance, one would say these Gleason scores look like those that are seen for U.S. patients that frequently are managed by surveillance. But our concern is that, based on the data where we could compare tumor histopathology across the European or the non-U.S. studies and the U.S. studies, we felt that these patients had under-reporting for poorly differentiated tumors. Clearly, there was a difference in reporting, so that even though these Gleason scores would be very comparable, I believe, to what type of patient might be a candidate for "watchful waiting" presently in the U.S., we believe that these scores are unreliable and, therefore, we can?t conclude that these patients had the same type of tumors as those patients that are frequently given the option, or at least advised that watchful waiting would be a reasonable option for them.

Although we agree that there was no assessment bias in the bone scans -- in that if you look at the number of positive scans that were read as other than positive, it was the same in both the

Casodex and placebo groups -- we are concerned over the fact that at least in this re-read, 27 percent of the scans have read as positive in the Casodex, and placebo group were read as something other than positive. This causes us to have some concerns about the actual accuracy of the measurements. And bone scans, like all other indices of disease progression, were not re-reviewed centrally, nor by an independent panel.

The last efficacy topic that I?d like to review with you this morning relates to survival. And what I?ve summarized on this slide are the percentage of deaths related either to prostate cancer or other in each of the three trials. The data in the upper half of the slide are those data that were submitted at the time of the initial submission as part of the efficacy component of the application. And they had a data cut-off date of June in 2000. With the safety update, we received additional survival data, which had a cut-off date of September, 2001, represented in the lower portion of the slide, and I think we ought to focus on those numbers since they are more current.

If we look just at prostate cancer-related deaths, we can see that there are small numeric decreases in both of Trials 24 and 25, but that in Trial 23, we see just the opposite. There?s a small numeric increase. I think the conclusion is that there?s probably no impact on survival at this time in patients with prostate cancer.

And similarly, if we look at other events we again see a little increase or a decrease, depending on which study we?re referring to. And if we go to the bottom, the data represented in yellow, we can see that the differences within any study tend to be very small. And we would concur with the sponsor that at this time there isn?t any evidence that treatment with Casodex is having any impact on survival either way.

So, to summarize what we?ll call unresolved efficacy issues, we can lump these into perhaps three broad categories. The first category concerns the maturity of the studies, and since only 15.6 percent of the patients using the sponsor?s endpoints and analysis, or 9.3 percent using the FDA?s

preferred endpoints, have had an event of disease progression, we think that these are early studies. The results from these studies are quite early. And that the long-term benefit of treatment at this time is unclear in the absence of survival data, or a survival difference, or meaningful quality of life data.

The second category relates to the inability of the division to identify those prostate cancer patients in the U.S. who would derive benefit from adjuvant therapy. Post-talk subset analyses by the sponsor were inclusive or not supportive, and we also remain concerned about the lack of valid Gleason scores, which has made it impossible for us to fully characterize those patients involved in the non-U.S. trials.

The third area is what is the risk benefit ratio for immediate therapy or monotherapy in patients with localized disease. This time I?d like to spend just a little bit of my presentation to go over some of the safety observations. This slide shows the disposition of patients in each of the trials. And as

you can see, the percentage of patients who terminated prematurely exceeds probably 30 percent or more in all of the trials. And in some trials, the percentage is higher in the Casodex, in others it?s higher in the placebo group.

If we look at Trial 23, the U.S. trial, we can see that the patient terminations due to adverse events in the Casodex group far exceeded those in the placebo group. What the reason for this imbalance is, we don?t know, except for the development of those adverse events, which we?ll discuss in a moment. And actually, adverse events exceeded in the Casodex group was a greater cause for premature withdrawals in all the studies. However, as you can see in the European studies, disease progression was a more common cause for withdrawal in the placebo patients than in the Casodex-treated patients.

The most common adverse events, as you heard earlier, are those related to the pharmacology of the drug, its anti-androgenic or its estrogenic activity. And as a result of the drug?s pharmacology, 73 percent of the patients across all the trials

reported breast pain, and 67 percent reported gynecomastia. You can compare these to the much lower incidence in the placebo groups of 7 and 8 percent respectively.

Because of the high incidence of breast pain and gynecomastia, I?d like to focus on this adverse event in somewhat greater detail. The figure that I?ve taken from the sponsor?s integrated summary of safety in which the proportion of patients without event, in this case gynecomastia, are represented as a function of time. And, as you can see, that by approximately one year or so after the onset of treatment, about two-thirds of the patients have developed gynecomastia. This percentage increases slightly, but most of this occurs certainly within the first year of treatment.

A very high proportion, as I?ve mentioned to you earlier, of patients do experience gynecomastia or breast pain. We can see that across the studies, this was a complaint reported by 86 percent of the patients. And patients withdrew from the study because of gynecomastia in what we believe is a

significant number. Across all the studies, 16 percent of patients withdrew because of gynecomastia or breast pain in the Casodex groups, compared to less than 1 percent in the placebo groups. And in the U.S. trial, I believe this number was approximately 20 percent, even slightly greater.

The sponsor was able to follow a significant number of patients for resolution of gynecomastia. And what this slide does is summarize the number of patients, or list for us the number of patients who had gynecomastia at the end of treatment, and who also had post-treatment follow-up. There were approximately 1,500 of these patients, and in approximately half of these patients, some degree of gynecomastia persisted at the last follow-up exam. Breast pain, on the other hand, resolved almost entirely, and the percentage of patients that had residual breast pain was quite low.

We've heard earlier this morning about quality-of-life issues, and in these particular trials there wasn't any effort to really assess quality-of-life in any systematic manner. There was very limited

quality-of-life data. There was data on maintenance of sexual function in the study that was conducted in Sweden. And I have to confess, I?m personally a little bit befuddled by these data, because the data that I show before you here, I thought I had taken directly out of the sponsor?s integrated summary of safety again, and this would suggest that in these patients, both in the placebo and Casodex patients, there?s a very significant diminution of sexual function over time. And in the bar graphs that we saw earlier, they didn?t give this impression at all, so perhaps we have misinterpreted these data. Perhaps you could explain the difference.

But if we interpret these data correctly, it appears that in both groups in this particular population as assessed by this instrument, there was significant decrease in sexual function over time. Whether one can put any credence on these data we don?t know, because of the rapid fall within 12 weeks of treatment onset in both treatment groups.

In these studies, the incidence of life-threatening or fatal hepatotoxicity was similar in

both the Casodex and placebo treatment groups. However, as shown on this slide, there was an increase in what was defined as clinically relevant changes in ALT or AST or bilirubin levels in the Casodex patients relative to the placebo patients. And roughly anywhere from two ?- this difference was two- to four-fold higher in the Casodex patients relative to the placebo patients. There was also a greater percentage of Casodex patients who withdrew due to liver-related adverse events, perhaps two- to three-fold greater in the Casodex group, as well.

So in conclusion, a high percentage of patient reported anti-androgenic or estrogenic related adverse events, 86 percent of Casodex patients versus 12 percent of placebo patients reported gynecomastia or breast pain. Sixteen percent of Casodex patients versus less than 1 percent of placebo patients withdrew because of gynecomastia or breast pain. And gynecomastia persisted post-treatment in almost half of the patients.

Life-threatening or fatal hepatotoxicity was rare and similar in both treatment groups.

However, clinically significant or clinically relevant -- to use the sponsor?s terminology -- arises in ALT or AST values, and withdrawals due to hepatic adverse events were two- to three-fold greater in Casodex-treated patients.

At this time, I?d like to return the presentation to Dr. Shames, who will summarize our concerns about this particular application.

DR. SHAMES: Thanks, Scott. First, I want to tell you where we are in a regulatory sense. We issued a non-approvable letter for this supplement involving Trials 23, 24, 25, and in that letter, we stated that we wanted to see more mature trial data to find out ?- to answer some of the questions that we have before us today. We also asked that, if it were possible for the sponsor to get the slides from the foreign studies and really do Gleason scores, but we believed that the essential issue was that these were sort of post hoc subgroup analyses, and that there was hypothesis testing, and they should choose well-defined successful subgroups, and perform well-controlled trials after the results that they?ve seen

currently.

I just would like to take time to discuss ?- clear up an issue regarding the interaction of the FDA with the sponsor regarding these endpoints. In the notes that I can see as far back as it goes, there was disagreement regarding the ?- what we consider an objective endpoint, the protocol-driven bone scan as opposed to the more investigator-driven endpoints, which the sponsor used. That disagreement appears right from the very beginning, because we were concerned about the possible unblinding, probable unblinding, perhaps, of gynecomastia, and the fact that Casodex in some variable way in itself will reduce PSA.

Now let?s go on to the review issues, which are the core of the concerns that we?ll discuss in the questions. We are concerned about the small number of progression events, and even fewer survival events after three years, to draw conclusions about long-term use of Casodex 150. As mentioned several times, one of the key parameters used in the U.S. for disease staging -- the Gleason score -- was improperly

used in the non-U.S. trials. In addition, there was disturbing inconsistencies between the pathology and clinical outcomes between the three trials.

The data proposed to support use of Casodex 150 in the U.S. patients is based on retrospective subgroup analyses. As far as safety concerns, there was a high discontinuation rate, and Scott discussed the gynecomastia, possibly irreversible liver toxicity.

Certainly on the face of it, you would, you know, consider that sexual function will be decreased in people who are ?- men that are castrated. But on the other hand, we have other issues when we?re using Casodex. And in fact, it?s very unclear whether -- when we?re dealing with quality-of-life -- we improve it with Casodex versus castration, or placebo. As a matter of fact, in the paper that I mentioned before in The Annals of Internal Medicine, April 2000, which looked at a large amount of analysis of androgen monotherapy in advanced prostate cancer, the authors concluded that treatment withdrawal, the most reliable indicator of adverse effects are less with LHRH

agonists versus non-steroidal anti-androgens.

The review regarding safety is particularly concerned because this drug has the potential for being used in a very wide population. We had some other review issues. There is concern over the potential, as we've talked about, survival detriment is too early to tell, and we feel there may be evidence for us to be concerned about that, and there is some biological plausibility.

There is a question, as I just mentioned, whether Casodex has any quality-of-life advantage over placebo or castration. And Trials 23, 24 and 25 are trials which studied heterogenous populations with different treatments that reflect differing practice patterns in various global locations. Finally, although not a key issue, bone scan readings appear to be imprecise.

That's the end of our presentation, and thank you.

CHAIRPERSON PRZEPIORKA: Thank you, Dr. Shames. And the floor is now open for the Committee to ask questions to the FDA. And I'll start by asking,

could you explain briefly, please, why you would not accept x-ray results or biopsies as an endpoint for this study?

DR. SHAMES: Well, I think you mean ?- well, because I think they were ?- some of those were investigator-driven, and we?re concerned that there may been some selection bias. You mean, x-ray ?- you mean a precipitation of the x-ray, or the biopsy occurred because of some change in PSA or knowledge of what the control ?- what the arm was.

DR. MONROE: I guess I?ll expand on that just a little. The documentation for these other events was very inconsistent in the application. They weren?t assembled by the sponsor in any way that you could actually determine, in most cases, exactly what was going on. They were reported just as having occurred, and it was not possible to really decipher what these were. Some of these were local events, and some were distant events. And without having had more documentation as to the nature of these other events -- forgetting about whether they were driven by factors or not -- we just couldn?t place any reliability on

them. And I did address the fact that there was no central review of these. There was no clear criteria in the protocols defining what some of these events needed to be. I believe some of these events may well have been enlargement of the prostate, perhaps, for those patients in the "watchful waiting" group. Yet, we couldn't find anything that said it had to be an enlargement by a specific size or not. It seemed to be driven only by the assessment of the investigator that an event of progression had occurred.

CHAIRPERSON PRZEPIORKA: Dr. Cheson.

DR. CHESON: Well, I can see the issue that you're raising about the size of the prostate, but a positive biopsy is a positive biopsy. No matter what drives it, it's evidence of progression. And even a positive x-ray is a positive x-ray, but that raises the other point, which troubles me no end, that there wasn't any central review of the x-rays. And I really find that hard to believe.

If I could ask one question which sort of came to me, because often we miss therapeutic leads

because they?re hidden in toxicities and whatever. Did either the agency or the company look to see if there was any correlation between the development of gynecomastia and outcome, because this may tip you off as to whether this is really a biological effect, and may be a plus instead of its being a minus. But I?m agreeing with Donna, that it?s sort of bothersome that you?d sort of write off things which are not subjective, and are purely objective, like positive biopsies and things, which I think, you know, in all fairness probably are evidence of progression.

CHAIRPERSON PRZEPIORKA: Dr. Krist.

DR. KRIST: Going on the theme about the sponsor's versus the FDA?s endpoints, to a certain extent I disagree. I mean, I do think an objective result is an objective result. There?s a higher risk of missing those objective results in the placebo patients because you might not look for it. But that?s something that I think is a difficult thing to think about.

I?m curious, though. You presented data showing that if you looked at just Trial 25 in the

"watchful waiting" group, and looked at low-risk people by FDA endpoints, that there was no benefit. And then you also showed in 24 looking at the prostatectomy group who are high risk, and by sponsor?s endpoints, that there was a benefit. I?m curious for Trial 24, if you were to believe in the FDA endpoint, if high-risk FDA endpoint and prostatectomy, if there was a relative difference, I didn?t see that number.

DR. MONROE: I think I?m going to have to ask you to go through that step by step, please, and then I can address each piece of it.

DR. KRIST: The big question I had was that you showed a slide doing the subgroup analyses, and you showed that on Trial 24, in the patients who had locally advanced or the high-risk disease, who had prostatectomy, and you went by sponsor?s endpoints, that there was a difference in outcome between Casodex and placebo. And I?m interested in Trial 24 for that same group, instead of going by sponsor?s endpoint, but by FDA endpoint, for Trial 24 who are a high risk, who had prostatectomy ?-

DR. MONROE: We?re talking about the

adjuvant treatment prostatectomy patients.

DR. KRIST: Yes. Right.

DR. MONROE: Okay. And on the slide that I showed, and we?re not set up to immediately go back, but I believe on that slide, which is ?- let me just find that for you so you can all look at it here. Were you talking about Slide 26, perhaps? Could you refer me to the slide on the handouts? That was the high risk prostatectomy FDA analysis. Is that the one you?re referring to?

DR. KRIST: Yeah. Is there a confidence interval for that? Is that statistically significant?

DR. MONROE: Well, there?s clearly nothing there. We could show you what those data look like if you use the sponsor?s analysis, if you wished. In other words, you would find events due to this category of other objective events, which would have an impact on the absolute numbers. Is that what you?re asking?

If you want to go to the backup slides, Randy. Okay. That?s the same data, I believe, but using the looser definitions where you

would include all events. And you would see, we have more events, and we see that there are some numeric differences, only one of which by this analysis has a confidence interval that is less than one. But if you go to the next slide and look at what?s driving these, I think this may answer your question. That?s Study 23 at the top, so we can see there?s actually one more positive bone scan in the Casodex group than in the placebo group. There were two more other objective events, and I can?t tell you precisely what those were at this moment. And there appeared to be four deaths, but those deaths, three of the four had nothing to do with prostate cancer. So it seems that as you go into these subset analyses deeper and deeper with small numbers, you can come out with almost any kind of an outcome. And that is what?s being driven by these.

I think perhaps the most compelling data were those of the sponsors using the criteria that they are now using for high risk, where we have a lot of events occurring, but yet there was no difference between the two groups. And if we could go back to slide -- I guess it?s 30. And here we don?t have to

bicker over whether we should or should not include these other objective events. This includes all of those other non-bone scan driven events, and there is just no difference in the ratios between the Casodex and placebo treated patients in Trial 23.

CHAIRPERSON PRZEPIORKA: Dr. Cheson, did you have a follow-up?

DR. CHESON: I was ?- this is just probably not even a very smart question, but I just want a point of clarification. There were those patients in the ?watchful waiting group?, who were treated on the basis of the PSA that went up, which have been alluded to as, perhaps, protocol violations. How did you handle them in the analysis? Did you include them? Were they censored at some point, and does that make any difference?

DR. MONROE: Neither we nor the sponsor handled them any differently. This question of whether or not they should have been included was not addressed at all in the sponsor?s original submission. And because of the fact that our basic analysis had not yet shown -- or maybe never would show -- that

there was a statistical difference in at least the "watchful waiting" local patients, it wasn?t pursued further. If he were to look at all of the watchful waiting patients, Stages 1, 2, 3 and 4, as a group, they do show a statistical effect as a consequence of Casodex treatment, but those ?- but one has to remember that there are many more events occurring in the T3 and T4 patients, and once those are removed, you have many less events to assess whether the change is statistically significant or not. And that is what we saw with our analysis based on the low risk component of the "watchful waiting" population.

CHAIRPERSON PRZEPIORKA: Dr. Albertsen.

DR. ALBERTSEN: My question drives to the choice of endpoints for these trials. In some respect, it?s almost an artificial construct in contemporary urologic and oncologic practice, in the sense that a bone scan and a survival are really downstream endpoints, to the point of 10 years and almost 15 years later when you look at some of the data in the literature. And my concern is: by excluding PSA progression as a potential endpoint,

don?t we potentially run the risk of missing a benefit, in the sense that if patients -- specifically in Trial 23 -- move on to LHRH agonist therapy when they have PSA progression, this happens before they even have a chance to achieve the endpoint the FDA is looking for. And, therefore, asking for more mature data, while very valid, probably puts that off until about 10 years from now. And I?d like your comment on that.

DR. SHAMES: Well, as you know, that?s sort of a controversial issue, and we have yet to have the hard data that we felt we needed to use PSA as a surrogate endpoint essentially. So we have not yet accepted that. I mean, that?s still being debated internally and externally, as you know. It?s a somewhat difficult issue. I think the ?- okay. Go ahead.

DR. ALBERTSEN: But the whole decision before us rests on that very decision, because the trial is clearly too short to demonstrate an effect from anti ?- at least in my opinion -- to direct an effect from a hormone therapy given over two years, given the lead time of five years. At a minimum lead

time of five years that PSA testing has achieved, we are identifying patients in the U.S. considerably earlier than our European and Scandinavian colleagues. We?re operating on them, so an adjuvant trial based on those patients given for only two years, I think at virtually any endpoint you select, it would be difficult to demonstrate the difference.

So the trial, as constructed, is stacked heavily in favor of not demonstrating efficacy, unless you ran that trial for a period of ten years. And I?m not sure if the FDA or the sponsor were prepared to do that up front, and we?re stuck now deciding what do you do with the information at hand.

DR. SHAMES: Well, I mean, we grapple with this issue daily because prostate cancer has this particular problem. We do trials regarding prevention of prostate cancer. And so, you know, perhaps if we had had ?- the problem that we have ?- the essential problem we have here is how to communicate who these people are that we can ?- that physicians will prescribe medication. And basically, although there are certain aspects, there are certain data here that

shows a difference, there?s no question about it. We could?- we?re not able with the data before us to, we feel, adequately communicate to prescribers who exactly is supposed to get this medication, and make sure that we weren?t giving it to patients too early, and they were taking this for years and years, you know, without ?- we don?t know, perhaps possible adverse events -- or giving them later where they might overlap with the patients that might have some survival disadvantage.

So that, you know, as you?ve seen in the questions, and we?ll discuss the questions. That?s part of our basic difficulty here.

DR. ALBERTSEN: If I can follow up, I think realistically were this drug, if it were to take ?- if FDA were to give its approval, I doubt it would be used as the indications are listed. Realistically, I think what would happen is most urologists and oncologists would give this drug to patients who demonstrate aggressive PSA doubling time. Specifically, if you refer to the Pound data from JAMA, anyone with a doubling time greater than ten

months is at great risk of disease progression.

I suspect this drug is going to be used as a substitute for another drug that is not indicated for use in early prostate cancer, but is uniformly used in this country, specifically an LHRH agonist. The risk factors for them is the potential for osteoporosis, and all the other complications we all grapple with. So, therefore, the average clinician is going to try to weigh the complications of one drug that?s not indicated with another drug that?s not indicated. Realistically, that?s what?s going to happen. And I kind of scratch my head looking at the data presented, and feel I?m kind of an artificial construct, or an Alice in Wonderland scenario. In fact, what we?re discussing bears little resemblance to what will happen the minute this drug gets approved. Your comments on that.

DR. SHAMES: All right. Well, that happens all the time. That?s part of the problem we have here, actually. Part of my concern is that the drug will not be used the way it should be used. And we will have ?- and I did say we might have hundreds of

thousands of men using this drug, in either late stage, early stage, in-between, when we have some indication that there might be in some people a survival disadvantage, you know. And so that?s right, absolutely. That is absolutely one of our concerns. It?s always one of our concerns, but in this case, given the huge potential population that could be using this drug, we?re concerned about it not being used in the right population. And that?s why -- since we had a lot of difficulty determining who exactly this should be used in -- that?s why we?re not ?- one of the reasons we didn?t approve it. We couldn?t rely ?- conceptually, of course, we realize people in Europe and Sweden are not biologically different than the U.S. I mean, obviously that wasn?t the problem. The problem was, the data were difficult for us. You know, we didn?t understand the problem with the pathology, you know, the internal inconsistencies.

The thing with the Gleason score, you know, was difficult. That?s one of the reasons we asked the sponsor to perhaps, if it?s at all possible, to get the slides, and better define the population.

That?s what we?re trying to ask there.

CHAIRPERSON PRZEPIORKA: Dr. George.

DR. GEORGE: I had a question about the further follow-up, and I guess it?s related to the definition of the primary endpoint, as well. How would you ?- if you do further follow-up, which is, I think, certainly needed -- if you do that, what are you going to gain unless you expand the endpoint some to ?- if you?re going to include bone scan only, you?re going to have some issues there with people who have clearly progressed, but just didn?t have a bone scan yet. And you?re going to have also issues of requiring a bone scan at future times. Have you thought about that, I mean, beyond the two years? I mean, if you just said two years, then there?s not much point in following up beyond two years, if that?s what your major endpoint would be. DR. SHAMES: Well, quite frankly, I was ?- I wonder if I?ll often see what happened to survival ultimately. I mean, that was one of my main reasons for asking for follow-up. I?m not sure there?s going to be a tremendous difference.

DR. GEORGE: Well, one of the things that was presented in the FDA presentation was, further confirm that the durations of the time-to-progression information is maintained, and that?s more than just survival. I mean, I agree certainly with the survival, but the ?- you?re going to have to think hard about ?- that endpoint thing is not going to go away just with further follow-up.

DR. MONROE: If I could just comment. The sponsor has indicated that these protocols do require bone scans at two-year intervals, so objectively they should be done in any patient who has not had documented objective progression at years four and six, as well. So that should provide us with additional evidence of disease progression or lack thereof in a relatively unbiased fashion.

DR. GEORGE: That?s good. Would you do a bone scan in someone who clearly has progression, I mean, that you already know has progression? Is at advanced stage and, you know, you just didn?t do the bone scan. You did other things.

DR. MONROE: You?d have to ask the sponsor

exactly what they?ve told their investigators. It was our impression that these were supposed to be confirmed by bone scan to address the concerns about not being able to maintain blind, but they would need to address that.

DR. CARROLL: Kevin Carroll, AstraZeneca Statistician, just to answer the question. If you could just repeat that question. The shock just confused me for a moment.

DR. GEORGE: I was just concerned, I guess if bone ?- it says that bone scans are supposed to be done every two years. If you didn?t do a bone scan because a patient had had clearly advanced disease because of other markers, and maybe died even of ?- I guess the death would be the endpoint, but you still would have had ?- presume if you had done a bone scan earlier you would have spotted it, but you didn?t. And I just wonder if there are going to be patients that you?re going to end up not counting as progression that were clearly progressions?

DR. CARROLL: Thank you for the clarification. What the protocol required was that in

patients who had not previously progressed, then a bone scan was scheduled at every two years. There was no intention to ?- for a patient who progressed, say, at three years, to then do a bone scan at four years if that would not be clinically indicated.

DR. GEORGE: Right. But that then gets to be a problem in the FDA. Okay. If it were ?- but it wouldn?t have been picked up as via a bone scan. It would have been a rising PSA or something, I think, what they?re talking about.

DR. MONROE: It was clear from the beginning that both the sponsor and the FDA said a rise in PSA would not qualify. There was never any issue that PSA increases would be considered objective progression.

CHAIRPERSON PRZEPIORKA: Dr. Redman.

DR. REDMAN: Just to reiterate on the endpoint, and really just ask the FDA directly, if I was coming to them with a trial of an intervention in this setting, you?ve agreed that PSA is not valid. You?ve shown data that you don?t accept bone scan because of the inherent error in bone scan that all of

us who practice are well aware of, that it?s very difficult to read a bone scan that?s not attached to a patient and interpret it. So I guess other than survival, overall survival, what endpoint is acceptable if you ask the sponsor to redo the trial, narrowly define the patient population. What is the end point going to be?

DR. SHAMES: We showed some of the problems with bone scan, but I don?t think we said we wouldn?t accept that as a protocol defined bone scan in everybody. A situation where we ?- in this particular case, and perhaps some of the advisors can comment on this -- we were concerned about, particularly with Casodex because of this unblinding issue. So there?s some issues that are particular here that may not be relevant to, you know, other trials with other drugs we?re not as concerned about unblinding.

The unblinding in the question of what the effect of Casodex is perhaps on PSA, and that kind of thing. What exactly the effect is, you know. Is it a variable effect? Does it change its effect over time, you know, things like that. So I think that this

particular drug has particular issues, which might not be in other drugs.

CHAIRPERSON PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: This is a follow-up to the comment that was made about patients who have a rapidly rising PSA, have the option right now. They get an LHRH antagonist, but Casodex is commercially available in the United States at a 50 milligram tablet, and I?m pointing at the open form. At least one patient who is taking 150 milligrams a day. This is a question to the urologists, either here or from the sponsor. How frequently is this therapy being used now in this area? Do we know anything about that at all?

DR. ALBERTSEN: I?ll just make an anecdotal comment. I know it?s beginning to make its way into the medical community. How pervasive it is, I think, depends on how close you are to a center that?s promoting it, or to an individual person who might be promoting it. But I think the very real issue is, as the long term concerns over LHRH agonists, which have become the de facto treatment for

men with rising PSAs, could Casodex be the substitute? And that?s the reality that?s playing out on the street. But I have no idea how prevalent it is yet.

DR. KELSEN: I understand. My question was, it seemed like that might be a default position, and certainly, we need to address the indication issue.

CHAIRPERSON PRZEPIORKA: Mr. Ohye.

MR. OHYE: Thank you. I have a rather fundamental question about the change in endpoints. Some people say I?m older than dirt because I?ve been attending ?- before I retired I?ve been attending End-of-Phase-2 meetings, dozens upon dozens of them. And at the conclusion of the End-of-Phase-2 meeting, the sponsor generally goes away with a good idea of what would be needed to register the drug.

If I look at the history of this product, they had that End-of-Phase-2 meeting in 1995, and -- was this division in existence in 1995? It was not. It was the Metabolic and Endocrine Division then. I believe the practice then was to allow the sponsor to carry away key elements of agreements made, and then

they would come back with a protocol based on the agreements made, sort of a quasi contract with the division. And it appears to me from the record, that they did that. And over the course of the next three years, they completed enrollment. And then a year later, the target was moved, and I think it would be very instructive for me as a representative of industry to find out how the heck that happened. Because, you know, these studies ?- you?re talking about a huge study here, costs millions of dollars. I?m sure you all are operating on good faith, but this moving target is quite troublesome to me personally, and I?m quite sure to others. I have other questions, if I may, but this is just a fundamental procedural question.

DR. SHAMES: You?re absolutely right, in that when people come for an End-of-Phase-2 meeting we do everything we can to make sure that everything is appropriate so they can do their trials, and we?re all in agreement. You know, we ?- there was disagreement about a lot of these issues since we?ve been here maybe the last three or four years, so I cannot say if we

would have ?- those of us here would have agreed to all of this, you know, the three different trials with the totally heterogeneous groups and that kind of thing. And certain other ?- we would have advised perhaps about Gleason scores, or central readings, things like that. So it was pretty much after the fact that we got here and looked at the trials and found the problems.

Now it brings us ?- and I agree that it ?- the overall procedure should be that we stick to the ?- what we say at the end of Phase 2, and then we let them go and then evaluate it.

Now sometimes people don?t ?- and I don?t know if that?s the case here. Sometimes that doesn?t happen anyway. You know, we can?t stop trials for sign problems. However, we are faced with this situation at it occurs now. I agree with your point and, you know, the only thing I can say is perhaps the people that reviewed it had a different view than we did, you know. It was before our division even was assembled.

But the issue before us is what we have to

deal with right now, so that?s, you know ?-

MR. OHYE: But nevertheless, we deal ?- as sponsors we deal with the agency as an entity, and as not just individuals? opinions, but we deal, you know, with the FDA as a whole.

DR. SHAMES: Your point is very well taken, and I absolutely agree that the procedure should be that we come to agreements at the end of Phase 2, and hold to those agreements unless there?s some scientific reason that comes up later that causes us to have a problem.

MR. OHYE: I think we all agree if there?s an overwhelming scientific reason to change prior commitments, but if we deal as sponsors deal with the agency as an entity, then we should be able to rely on prior commitments.

I have a question for Dr. Monroe. I?m sure you weren?t implying -- and I just want to make this clear -- that there is anything wrong with the sponsor proposing a change in indication, because that goes on, you know, frequently during the development of a product. I just want to make sure that I

understood that right.

DR. MONROE: Well, the need to change an indication does come up not infrequently, where an indication has to be modified to best reflect what the data are. What we were, I think, trying to convey to you is that, in an effort to identify who would best be served by the use of this drug as we reviewed it and brought up these issues, the indication was changed on multiple occasions, because the data clearly didn?t support certain things. Adjuvant issues in early disease, and we were surprised that the application even came in with such a broad indication, because there was just no data to support that. When those issues were brought forth, the sponsor acknowledged that and made these changes which perhaps could have come in initially.

And that I think it?s also a reflection that I don?t believe that we or the sponsor -- I shouldn?t really speak for the sponsor -- has adequately characterized who would benefit by adjuvant therapy. On that last slide I showed, we pretty much took aside all of the issues about what the endpoint

should be. And those data I showed, they showed absolutely no effect of Casodex in U.S. Trial 23, based on the sponsor?s present definition of high risk. And it?s our concern that -- let? say the drug were to be labeled as that, and you say high risk. Well, are you going to define what high risk is, or are you going to leave it to each practitioner? I don?t know.

But if you use criteria that I think are generally accepted, as we use our high Gleason score, post-operative PSA, and a high pre-operative PSA, we didn?t see any benefit of the drug. And that?s our dilemma. We just don?t know who would be served well by taking this drug.

MR. OHYE: I beg the Committee?s indulgence. I have two short questions, if I may continue. I believe I heard the conclusion that some of the data didn?t support a clinical benefit when you were making reference to some of your slides. This may be useful for deliberation when we discussed the questions. Are there data likely to predict clinical benefit?

DR. SHAMES: Let me go ?- first, I would

like to go back to the other issue, because Dr. Hirsch reminded me that in 1995, because he looked this up, we did not ?- we discussed the issue of the endpoints and did not totally agree with the endpoints actually, and the endpoints were ?- and as I said, you know, we can?t stop trials for design problems. We can only stop them for safety problems. Can you repeat the question, because I ?-

MR. OHYE: I was making reference ?-

CHAIRPERSON PRZEPIORKA: I?m sorry. Before you go on, can I just address that, please. Just switch hats as a former member of an IRB, and to encourage you to re-look at that issue specifically, because from the IRB point of view, to put a patient on a trial which will not give you an answer is a safety concern.

DR. HIRSCH: The issue is one of bias, of limiting bias. In 1995, the company was informed that there was a high likelihood that there would be a high incidence of gynecomb in the treatment group, and that that might unbias the trial. That was clearly stated and acknowledged by the sponsor, and it did come to

pass. And in an effort to reduce bias, we discussed with the sponsor alternative endpoints that might be less apt to bias. And that was, to the best of our knowledge, one bone scan that was done in everyone at year two, so at end of Phase 2, we held these discussions with the sponsor.

DR. BRAWLEY: Can I ask, was there an ?- pardon me for interrupting. Was there an agreement between the FDA and AstraZeneca about what relevant endpoints would be for these studies that would lead to approval?

DR. SHAMES: Since my ?- I have been there in various capacities -- we could not totally agree. We knew what the endpoints were, but we did not agree about these other endpoints, the objective progression endpoints.

MR. OHYE: I?m afraid I?m taking too much time, but one last question, if I may. I was trying to ask -- I remember hearing the conclusion that the data didn?t support the finding of a clinical benefit. My question was, and I thought this might be useful when we go into our own deliberation, were there any

data likely to predict a clinical benefit?

DR. SHAMES: I think an objective ?- however we defined it, an objective progression would be information that we would consider clinically important, or delaying objective progression in a way that was not biased.

DR. MONROE: Well, if I could add a little bit to that. The question of accepting the bone scan data is really not a question. I raised the concern that there is an inherent lack of accuracy in these methods, and we are concerned that a degree of inaccuracy needs to be considered when you?re looking at small absolute differences between treatment groups in trials that show very few events. We?re not saying that the bone scans are not acceptable as an assessment. We think that was a very valid endpoint, and would be done in a way that would be subject to minimum bias.

I think we would accept other possibly objective endpoints if they had been well documented, and had been confirmed by some type of a central reading, as is frequently done in oncology trials.

And all of that was lacking in this particular trial.

MR. OHYE: I?d like to reserve my comments for the general discussion. Thank you.

CHAIRPERSON PRZEPIORKA: Dr. Blayney.

DR. BLAYNEY: I have two things. One gets to the issue of bias, as you put it, or this unblinding effect by Casodex, or unblinding effect. When you?re treating a patient, was your concern that gee, Mr. Smith, you have gynecomastia. You must be getting the active drug, and we?re going to ignore this urinary retention, or this new bone pain, or this rising PSA. Whereas, in somebody who is not having gynecomastia, they?re treating investigator would jump on a similar symptom in some differential manner.

DR. SHAMES: I think it?s the general issues that we?re concerned about, regarding bias. You know, whatever ?- if you know that 80 percent of the patients ?- if the trial is essentially unblinded, then it?s not the kind of trial that gives us the same kind of data as a blinder trial, and we were trying to get the best data possible.

DR. BLAYNEY: I mean, the endpoints you

showed seemed to be very unsubjective. I mean, death, bone scan progression or some other PSA progression seemed to be uninfluenced by observer interpretation. So I think the suspicion or the concern that you had in setting an endpoint that gynecomastia or some clue that a patient was getting active treatment turns out to be ?-

DR. SHAMES: Well, it?s true that death and bone scan are ?- we accepted death and bone scan. And PSA is a separate issue which, you know, needs other discussion. We don?t have the data right now to use it as a surrogate endpoint, and many of the other events were driven by the investigators.

DR. BLAYNEY: But I?m saying that I don?t see that an investigator would have that ?- would be biased by the ?- he?d do the same ?- an investigator is likely to do the same thing, regardless of whether he thinks the patient is getting active treatment or not.

DR. SHAMES: Well, I guess I would disagree about that.

DR. BLAYNEY: Fair enough. The last thing, I think, you?re asking us to make a judgment

here basically on subset analysis since 1995 and this inauguration of the trial. You said well, wait a minute. Let?s now retrospectively or encouraged the sponsor to retrospectively define a group of men whom they thought might benefit based on a retrospective subset analysis. That?s something that has been looked at askance at this committee level, and I?d like to hear why you would want to do that.

DR. SHAMES: Why we did subset analyses?

DR. BLAYNEY: No. Why you would encourage the sponsor to bring forward an application for an indication based on a ?-

DR. SHAMES: No, it was not a sub ?- what they brought ?- their original indication was essentially everybody in this trial. Their original indication was everybody. Everybody who doesn?t have metastatic disease was the original indication. We didn?t think that was reasonable. However, the data supported it. And we?d said that and they went and tried to find the appropriate subgroups. And, you know, we are ?- you know that?s what happened.

DR. BLAYNEY: And based on that, you know,

we might as well just go home, because they haven?t demonstrated that. But I think there?s efficacy there that we need to ?- I would encourage you all to find a way to take care of ?-

DR. SHAMES: Actually, the advice we?re looking for here, I mean, quite frankly, we are ?- you know, I said this to the sponsor. We could not figure out how to communicate who these people are to be treated with this medication. That was our basic problem, because there were various trial design problems, aside from the pathologic problems, et cetera, et cetera. And that?s reflected in the questions, and we certainly didn?t want to go approving this for everybody since this is not a totally benign drug, at least what we know about it.

DR. BLAYNEY: I think Dr. Albertsen?s comments are right on point. It?s likely to be a drug that is used as a substitute for another non-approved drug. And this is going to be an expensive drug that patients will have to put that into their and their physician?s calculus.

CHAIRPERSON PRZEPIORKA: Dr. Brawley, do

you have another question? Dr. Hanno.

DR. HANNO: Just two very quick points. One is, since the bone scan data is so critical in this, I really think that some confirmation of which of the bone scans are truly positive would be helpful in at least calculating the absolute risk, because it may be much lower than it appears in these data. And there are plenty of studies that show how bone scan data is kind of unreliable. Even though it may be the same unreliability in both sides, it doesn?t mean that the risk is significant.

Second, aren?t we ultimately talking about if we?re going to use delay in objective progression as the endpoint and agree to that, don?t you really need an answer on whether immediate hormonal therapy versus delay, versus intermittent hormonal therapy? Which of those ?- is there a problem between them? I mean, that?s really the underlying issue here that we don?t have an answer to, and that we?re sort of skating around, I think. And in the absence of that, you?re really looking at survival and quality of life data.

CHAIRPERSON PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: Yeah. Seeing that there was someone from AstraZeneca that wanted to respond to one of the questions I asked earlier, is that allowable?

DR. SCOTT: Ask the question again, please.

DR. BRAWLEY: Well, I was asking what was the FDA and AstraZeneca?s agreement back in 1995. And it just seems somebody had gotten up ?- I just saw him out of the corner of my eye, and they weren?t allowed to speak.

DR. SCOTT: Mark Scott, AstraZeneca. If you ?- the interpretation of the minutes is there were a couple of different endpoints that were under debate. We designed the Casodex clinical trial program as one large program, where the analysis we proposed was based on objective progression as we defined it in each trial. The difference really was whether you would need to have two clinical trials to support that indication, if in fact it was time to progression.

The overall analysis could be done if survival was the endpoint of interest, but we focused

on clinical progression as the primary endpoint. And we agree that we did have the conversations about the potential for unblinding, but I believe that we?ve demonstrated in the application that blinding was not ?- or the unblinding was not present due to the frequency of the assessments being similar between treatment groups, and across studies.

CHAIRPERSON PRZEPIORKA: Dr. Hoberman.

DR. HOBERMAN: I have two points. One is that I agree with the sponsor that the issue of blinding is probably not a substantial issue in these trials. The results are quite robust in Europe, whether or not you take into account time to event or incidence of objective progression. The other thing has escaped my mind. I must have gotten a shock from this.

Oh, yes. I was just struck by lightning. One of the ?- and I?m very sympathetic to what Dr. Blayney said, because once we ask the sponsor to go back and find a subgroup in which there would efficacy, it was practically doomed to failure from the beginning, and the reason is that the U.S. trial

was a null trial. There was no room for anybody to get true benefit. And so what happened was that the sponsor went back and did what they could, and had a very, very small subgroup, which showed a leaning towards results that were similar in Europe. The problem is that it was based on so few results, so few patients that it simply wasn?t reliable, and it was hard to take seriously.

The slide that Dr. Monroe showed, which happened when you took into account more patients to try to increase the size of this high risk population, the whole thing blows up in your face. You?re including more people in a null trial, and the hazard ratio goes right back to one, so it?s sort of like a rubber band. You pull it out, and it?s going to snap back. So I think that in this data is futile to try to go back and try to find a believable subgroup of patients in the United States who actually benefitted from the drug. And we?re in this problem because we have something in Europe that is trying to be extrapolated to the U.S.

CHAIRPERSON PRZEPIORKA: Thank you. Dr.

Martino.

DR. MARTINO: This is terribly reminiscent of breast cancer. The real problem that I see here has to do with the fact that the gentlemen who were enrolled in America actually did too well to show you much of a difference if there could be one. It really comes down to that simple problem, which is in no way unheard of in adjuvant therapies. And I really think that?s at the gut of all of this, that the patients did so well that there?s no way, at least with this length of follow-up and this volume of relapse, which we?re really in the range of what, 5 percent or so for that one trial. In all fairness, how could you expect that there would be much of a difference unless you had a true miracle. And you can turn that data inside out and upside down, and it?s not going to change unless either you add more patients or more time passes.

The other issue is, you lost a third of the patients. Remember that they actually withdrew, which further reduces your number, so the real problem is unfortunately, or fortunately, how you choose to look at it, that the Americans did well.

CHAIRPERSON PRZEPIORKA: Other comments. Okay. Then before we break for lunch, we have two more individuals who want to respond at the open public hearing after hearing all the data, so I?d like to call to the podium first, Mr. John Page from Us Too! International.

MR. PAGE: My name is John Page. I?m President and CEO of Us Too! International. We are a 501(c)(3) prostate cancer education and support group. As a matter of disclosure we do, in fact, get funding from a number of sources. One of them is AstraZeneca, but do not interpret that to mean that someone has paid me to come here and make the comments that I am about to make, because any people that know me, know that that is probably the farthest thing that could be from the truth here. And unfortunately, I have not been in this kind of a situation before, so if some of my comments come out as too aggressive, please forgive me.

I am not, by the way, a prostate cancer patient, but I do work with them, have over the last three years on a daily basis, and so I speak really

more as a patient advocate, as opposed to some of the gentlemen this morning we who have spoken really from the heart, and having to deal with this full on. I have had access to the data over the course of the last year, and so I've had a good opportunity to look at it.

I am also someone who has worked in healthcare for the last 30 years almost, and have a science and engineering background, so I do have an appreciation for statistics and dealing with research, but I do not consider myself, thankfully, simply a researcher or statistician, so I'm really addressing you really from the human perspective. And in dealing with that from the human perspective, I think I look at this as trying to define do patients deserve the information that is contained in these studies.

I hear the FDA talking about their determination of who should get this drug, and perhaps it's just a generation that I have, but I find that not what I would hope the FDA would be looking at. I enjoy the FDA protecting me from bad things, and I enjoy the FDA giving me information that I can rely

on, but I would hope that people would recognize that as a patient, it?s really up to the patient and his or her physician to determine what course of action is best for them. I don?t know that anyone in this room who?s not having to make that decision on a personal level should be excluding information given to the patient. And I think that?s really the crux of what I see us talking about here, is will you allow information about this trial to be provided to physicians and patients, and have them make a determination about whether or not this treatment option should even be considered.

I enjoyed the comments about the real world perspective, and whether or not you are setting up an Alice in Wonderland reality, but from all intents and purposes from a patient perspective, PSA rise is, in fact, a de facto standard that a patient uses to determine whether or not his disease is progressing. Whether we want to argue about that in theory and in research terms, the reality of the practice is a patient goes to his physician when he sees a PSA rise and says I?m afraid my disease is

progressing, and I want to have another treatment. Good or bad, that?s the reality of the situation.

And I think the risk benefit equation can only be, and can best be determined by that patient and his family and his caregivers, because when it comes down to it, and you look at the NIH mandate that a patient be responsible for his or her care and the decisions thereof, the patient can?t make that determination unless they are given information. And there is no information that can be given unless this drug is approved. And so I find that by cutting off, prospectively cutting off even the discussion of potential benefit, and I think what I?m hearing after reviewing the data for a good number of months, and in listening to the FDA and AstraZeneca today, what I?m hearing is that there is definitely benefit coming ?- we?re trying to determine what group of patients that is, but there seems to me benefit, substantial benefit. Depends on how you define that, but at relatively small risk, and I think as long as the patient is informed up front about what those risks are, there seems to me very clear, and one of the

gentleman from the U.K. who talks to his patient about expecting gynecomastia or breast pain. I think that that?s really what should happen. The patient should be fully informed.

Whether or not that happens is really a clinical decision, but when you?re looking at 40 to 60 percent reduction in progress of this disease, to me from a patient?s perspective, that would be very significant. And when the risks are identifiable, potentially manageable, and this is not an irreversible ?- I mean, the patient can go off this if he chooses, or if he decides that it?s not something he wants to do, I think that that?s really a patient decision. And again, as a patient advocate, my point is empower the patient with the information to make that decision.

I will use one statistic, I guess, because I think that it?s important. There were at one time more than 100 men in this room. If we use statistics, my guess is 20 men in this room will come down with prostate cancer. If I use further statistics about recurrence, 5 to 10 of those men will have a

recurrence and potentially be seeking treatment options for which they have, at this point, limited or no treatment option availability.

Would you, if you were one of those five or ten men, want to prospectively eliminate a potential option with known risks. I guess that?s the question I leave you with, because as a patient advocate, a patient is really looking at options that are out there. When there are no options out there, and currently for a subset of patients, there are no treatment options out there, this represents a viable treatment option if they and their caregiver chooses to do it. And again, I think that?s the most empowering thing you can do today, is allow the patient to have the information upon which to make a decision that affects their life. Thank you very much.

DR. BRAWLEY: May I ask him a question?

CHAIRPERSON PRZEPIORKA: Yes, Dr. Brawley. Mr. Page.

MR. PAGE: Yes.

DR. BRAWLEY: Did I mishear you. Are you

saying that the FDA is keeping doctors and patients from discussing this data currently, and keeping doctors from prescribing this drug as an adjuvant therapy at present? Is that what you were saying?

MR. PAGE: Right now, Casodex 150 is not an approved drug, and it is not available, widely available. As a result, if it?s not approved, it really doesn?t even come up in conversation except as an off-label indication. And I think that if you are assuming that it is okay for us to continue to treat patients routinely in off-label activities, then I say by all means. I mean, you cannot approve this, but I think if you?re going to be open and honest, and the reality of the situation is, patients are looking for something that may give, as the data indicated, perhaps a two year disease progression free life, that?s a quality of life indicator that a lot of men are going to accept.

DR. BRAWLEY: Have we seen data that show that there?s a two year progression free interval with this drug?

MR. PAGE: I looked at the data that is

presented, and if you look at the Casodex versus the placebo, there is a ?-

DR. BRAWLEY: Really.

MR. PAGE: It may be one year, it may be two years, it may be three months. There is certainly what appears to be ?- and again, I?m going based on what the data is. The data does not appear to be contradicted by the FDA. There does appear even in the FDA analysis to be a benefit in time to progression. Their time to progression does not include PSA, but I can tell you, and Dr. Brawley, you probably know from your own practice, that a patient PSA rise is, in fact, a standard that a patient uses, whether the FDA or researchers choose to use that or not. It is, in fact, the de facto patient standard.

CHAIRPERSON PRZEPIORKA: Thank you very much, Mr. Page. Next is Mr. Ben Fay from the Wellness Community Delaware.

MR. FAY: I?m sorry to say good afternoon. I have no conflict of interest, but when I offered to come and say a few words here, AstraZeneca did agree to reimburse me for my out-of-pocket expenses.

I?m a retired chemical engineer from Wilmington, Delaware. In February, I?ll be a six year survivor of T4 node positive prostate cancer and I watched my father die a horrible and degrading death from prostate cancer. I?m the community coordinator for the Wellness Community Delaware. I?m a Director and Secretary of the First State Prostate Cancer Support Group, and I also volunteer at the American Cancer Society and Christiana Cares, the principal health provider in northern Delaware. And as part of Christiana Care?s Cancer Outreach Program, I volunteer with a group of African American men to promote prostate cancer awareness and screening.

In these roles I know and speak to dozens and dozens of men who have or are at risk of having prostate cancer. I think I can speak realistically about how men at the grass roots level feel about prostate cancer. And I will tell you, and I can speak very confidently of this, there are three concerns that men have related to prostate cancer, other than survival. The first concern is number one on everybody?s list, loss of sexual activity. Number two

on just about everybody?s list is incontinence, and number three, is hot flashes. Rarely hear any mention or concern of gynecomastia, and that?s a fact.

I?m simply going to build on what John said, and skip some of the things. I agree with everything he said virtually word for word. I?d like to talk about the African American community where I really am familiar. There are many men there who refuse to be screened or who avoid, or delay treatment after diagnosis of prostate cancer, because they fear loss of sexual ability. These men represent a self-selected and I think largely unidentified de facto group of watch and waiters. If these men had the 150 milligram dose of Casodex available with its very low level of adverse effects, adverse sexual side effects, they would elect earlier intervention, and thereby distinctly improving their likelihood of living longer and better.

And delay or avoidance of treatment is not limited to the African American community. Many Caucasian men who have had definitive treatment for prostate cancer, radiation therapy or radical

prostatectomy, and who now find themselves with a rising PSA, and this is a phenomenon clearly regarded by both the men and their physicians as a sure sign that their prostate cancer is progressing. Delay taking the next step, which is chemical or physical castration, and I meant to tell you that if I stumble during the presentation you can chalk it up to cognitive dysfunction or whatever you called that earlier, because as part of my treatment, I had an orchiectomy almost six years ago. And they do this, they delay the treatment because of the horror stories they hear about hot flashes, or because they fear losing whatever sexual function they still have.

These fears extend across the whole male spectrum. I?d like to give you three quick examples. Dr. Soloway talked about some patients from the doctor?s perspective. I?m going to talk to you about them from the patient?s perspective, and from my perspective. And I?m going to talk to you about three men that I know personally, that are friends, that I talk to. At the Wellness Community we deal with the emotional aspects of cancer. We talk, like you never

heard men talk. There is no secret unbarred in our discussions, but anyhow, one is an African American man. He delayed additional treatment when he had a rising PSA following radiation out of fear of hot flashes, just that, hot flashes. He allowed his prostate cancer to progress until it was untreatable, and he died, I think prematurely.

George, a Caucasian has a Gleason Score of 6 and a PSA varying between 15 and 20. He?s gambling on watchful waiting because he does not want the side effects of any currently used treatment. Lou is a 76 year old Caucasian who has radiation. On Monday night at our support group meeting at the Wellness Community, he was in tears as he described the pressure he gets from his 78 year old wife, new bride, when he loses his ability to have an erection following injection of an LHRH agonist, so he stops taking the injection. His erectile dysfunction, his erectile function returns. I did stumble, and his PSA rapidly climbs to 80 before he panics and resumes the injections and the devastating cycle restarts.

These men need the option of taking the

150 milligram dose of Casodex, and they need it now, not years from now when every I is dotted, and every T is crossed. The risk of taking it, as I read the data, is very small, and the potential benefit is great. Give us, the patients, the opportunity to make the choice. I beg you. I beg you to approve today?s application. Thanks.

CHAIRPERSON PRZEPIORKA: Thank you very much, Mr. Fay. Is there anyone else who has a comment to make? In that case, I want to actually thank both Mr. Page and Mr. Fay for their courage to do this after the presentations, and really address the data from a patient?s perspective, and come here to do that. Thank you.

We?ll break now and return at a quarter to 2. Actually, I?m sorry, 2:00, but Dr. Templeton-Somers wants to make an announcement first.

DR. TEMPLETON-SOMERS: One of the big advantages of holding an open advisory committee meeting is that discussions like these take place in an open forum. It?s unusual for this particular committee to have a lunch break in the middle of an

application, and I?d like to put forth a gentle reminder to everyone in the room that discussions of this application with the Committee should wait until this afternoon when our open meeting resumes and everyone can hear and participate. Thank you.

CHAIRPERSON PRZEPIORKA: So please return here at 2:00.

(Whereupon, the proceedings in the above-entitled matter recessed for lunch at 1:20 and resumed at 1:59 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:59 P.M.)

CHAIRPERSON PRZEPIORKA: Dr. Shames, you gave a very nice introduction to the questions earlier today, so unless there?s anything burning that you wish to add, I will dive right into it. Fine, let us dive. So we?re going to discuss Casodex for adjuvant therapy to radical prostatectomy and radiotherapy of curative intent in patients with locally advanced non-metastatic prostate cancer who have a high risk for disease recurrence or immediate treatment of localized non-metastatic prostate cancer in patients for whom

therapy of curative intent is not indicated.

We?ll go through the questions one by one, ask if anybody has any comments, and then call the question and take the vote, except for the essay questions, which I don?t think we have today.

Number one, across ongoing Trials 24 and 25, only 15.6 percent of patients using sponsored preferred endpoints, and 9.3 percent of patients using FDA requested endpoints had objective progression of prostate cancer or died from any cause in the absence of disease progression. At the time of data cut-off, June, 2000, median follow-up was 2.6 years in Trial 24, and three years in Trial 25. In the absence of meaningful survival data or quality of life benefits, are these studies sufficiently mature to conclude with a reasonable level of confidence that patients treated with Casodex in these trials will derive clinically significant long term benefit? If not, what additional information is needed? Dr. Krist.

DR. KRIST: Well, I ?- looking overall, it?s kind of tricky for me hearing both perspectives. I have some reservations with the subgroup analyses.

I have reservations with combining the data on the studies, and my inclination is to say it seems like there?s some form of a benefit, but I can?t put my finger on as to who it is. And I also think that whether that conveys into a survival benefit, there is some room for question with that, particularly with U.S. patients, because I think that the populations treated and diagnosed in the U.S. probably are very different than those treated in other countries.

CHAIRPERSON PRZEPIORKA: Any other discussion of this question? Dr. Kelsen.

DR. KELSEN: I think this is a question again to the urology, the advisers at the table. My impression is that although the 23 Trial in the U.S. focused on a different population, people undergoing curative therapy, that many patients in the United States are seen with the same stage of disease as patients seen in Trials 24 and 25. And it?s not that we don?t have patients in the United States who present with these states of disease or rapidly develop them, but we just didn?t ?- they just weren?t studied in this particular cohort. Am I correct?

DR. HANNO: I think you are correct. I think some of these patients get treated with the LHRH analogs, and I think that it would be more appropriate to compare it to that than to placebo, because a lot of these patients don?t get treated with placebo when they?re in that stage, or at least have that in the mix.

DR. KELSEN: But the population exists in the states.

DR. SCHOENBERG: Well, I think we should just have the caveat that although that?s true, we see a very significantly declining number of the more advanced stage disease, precisely because of the very proactive approach that the American medical community and patients have taken toward early diagnosis.

DR. ALBERTSEN: My concern in the indication is the term adjuvant, and then moving on to define high risk. I don?t think the data I?ve seen convinced me that true adjuvant use of this drug is sufficient since Trial 23 basically showed no difference. Where I begin to hedge a little bit is the question of high risk patients. And indeed, those

are more easily identified post surgery, when you begin to see a rising serum PSA. Unfortunately, they?re not the subjects of any of the trials, and they?re the ones of most interest to the urologists. As a consequence, I?m struggling on how best to interpret the trials of the more advanced disease, because I believe they do show efficacy. But then you have the question, are the European population sufficiently generalizable to the American population? I think they are, but I think the American population has just been identified a good five to seven years earlier, implying that you probably need to have people on this drug for at least five to seven years before you see the true survival differences, or at least the efficacy differences that you see in the European trials.

CHAIRPERSON PRZEPIORKA: Dr. George.

DR. GEORGE: I think it?s ?- the problem here is a follow-up issue, particularly on 23. And I think we do need further follow-up to be sure of what we?re getting. And one of the things in saying that, we?re in a situation where we would like to have the

answer faster. I mean, we would like to have fast answers, but we?re in a setting where it?s very difficult to do. It?s a long time before recurrence, and certainly before we have much information about survival. And that?s just a tough situation.

We?d like to have very good surrogate markers that would spot all this, but we don?t have them. And so my take on this is, these are very interesting results, but follow-up is a big issue.

CHAIRPERSON PRZEPIORKA: Dr. Redman.

DR. REDMAN: I guess the point here is significant long-term benefit. I think, you know, following patients in 23 for the next 20 years isn?t going to really answer because of the patient population. But if you look at the two European trials, I don?t think 2.6 or three years is adequate follow-up to say that there?s a long-term benefit versus a potential short-term benefit. I mean, it?s a quandary in oncology, do we treat you now with toxicity, and there is toxicity to this drug, more so than no treatment. Or do we wait until you develop symptomatic progression and treat you at that time for

?- you know, overall survival is a long-term benefit.

CHAIRPERSON PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: I would agree that the issue of long-term benefit is the real problem here, that just two to three years doesn?t do it. If there was a trial that showed that there was a survival benefit, that would be, in my mind, a slam dunk and very easy to recommend approval. But we haven?t even really proven that we make the patients feel better. We?ve shown some indications that show that maybe some of the patients feel better. And we?ve also shown that, at best, 85 to 90 percent of the patients who would be treated wouldn?t even need therapy to begin with, and 30 percent of folks are going to drop off, so I guess I have some real problems and reservations here.

CHAIRPERSON PRZEPIORKA: Dr. Martino.

DR. MARTINO: I think I have a different reaction to this than what I?m hearing around the table. These are patients where the word adjuvant, I think, does apply. They are patients without obvious distant metastases, and we?re looking at their first suggestion that they have metastatic distant disease.

Okay? That is the adjuvant setting. And what you normally see when you do adjuvant trials is you don?t see survival advantage until years later. You tend to see that there?s a difference in terms of when patients have their first evidence of recurrence.

I think that?s what you?re seeing in Studies 24 and 25. You?re not seeing that in Study 23. Many of us could have almost predicted that you wouldn?t see it this quickly in that particular U.S. trial. So for me, there really is nothing here that disagrees with what I recognize is a basic principle, that this is a hormonal disease where hormonal therapy to a small degree, which is the problem with all of our adjuvant trials. It is that 2, 3, 4 percent if you?re lucky, that you see a difference between a treated and untreated group. So I think for me, there is value to this therapy in the patients that were treated with it, which is what the question states. The issue of whether that can be translated to the American population is a different issue for me.

CHAIRPERSON PRZEPIORKA: And I think I want to echo what Dr. Martino says. If you do look at

the curves, they do separate. And if you follow the curves long enough, eventually all the curves will go to zero, and so we have to figure out what does long-term really mean in the life of an elderly patient or a young prostate patient. And so some of the curves were very definitive, in not just P-value but size difference, the interval difference between the placebo group and the treatment group. Dr. Brawley.

DR. BRAWLEY: Yeah. That gets back to an earlier point. The reason why we don?t see median time to progression in the two arms is neither arm has actually lived to median time to progression yet. That really means that we?re not treating very much at this juncture. I mean, if there is a benefit, and the advocates really need to understand this. You know, if you?re talking to that black guy up in Connecticut, you need to tell him there?s a one out of 25 chance that this pill may help you, and a one in three chance that you?re going to drop off the pill because of side effects. You really need to tell him that.

CHAIRPERSON PRZEPIORKA: Other discussion? Then I?ll call the question once again. Across Trials

24 and 25, only 15.6 percent of patients or 9.3 depending on endpoints had objective progression of cancer or died. At the time of cut-off median follow-up was 2.6 and 3.0 years. In the absence of meaningful survival data or quality of life benefits, are these studies sufficiently mature to conclude with a reasonable level of confidence that patients treated with Casodex in these trials will derive clinically significant long-term benefits? Dr. Redman.

DR. REDMAN: No.

DR. BLAYNEY: No.

DR. GEORGE: No.

DR. CHESON: No.

DR. ALBERTSEN: No.

DR. REDMAN: No.

DR. KELSEN: Yes.

CHAIRPERSON PRZEPIORKA: Yes.

DR. KRIST: No.

MR. ANDERSON: No.

DR. SCHOENBERG: No.

DR. BRAWLEY: No.

DR. HANNO: No.

DR. PELUSI: No.

DR. MARTINO: Yes.

DR. ALBERTSEN: No.

CHAIRPERSON PRZEPIORKA: That?s three yes and 13 no. Question two, do the data that is clinical stage PSA level and lack of valid Gleason Score from Trials 24 and 25 allow for the adequate definition of a patient population that can extrapolated from the non-U.S. studies to a defined group of U.S. patients who will derive significant benefit from Casodex therapy?

DR. CHESON: Point of order, there?s a second part to the first question that wasn?t addressed. If not.

CHAIRPERSON PRZEPIORKA: Oh, sorry. Thank you. If not, what additional information is needed. Yes, thank you. Would you care to take that? Dr. George.

DR. GEORGE: I?m the one who noticed that. He?s the aggressive one who spoke up, but I had ?- I thought we were going to address that because that was an important part if we did say no.

CHAIRPERSON PRZEPIORKA: Yes.

DR. GEORGE: And to me, again getting back to the follow-up issue, and it?s still the ?- what are these types of information we can maybe talk about later I guess, number two, and so forth, but the key with respect to follow-up is to follow-up until the number of events is higher, the percentage of events. I won?t go through all that again, but it?s still, even in the ones like 025, it?s still a low percentage of overall events. And events I?m talking about here are either death, bone scan progression, or even this other progression. You just add them all up, especially in the death category, of course, but in the others as well. The overall percentage is still low enough to be disturbing - not disturbing, but to be unreliable with respect to the long-term issues. Even though I agree that unless you change definitions of endpoints, the early results aren?t going to change. But we do need to know the long-term, even granted that everybody either dies or progresses eventually. You still want to see what happens later, and have more reliable answers. So the kind of information I

would say we need first and foremost, is a higher percentage of events in all these categories.

CHAIRPERSON PRZEPIORKA: Dr. Cheson.

DR. CHESON: Yeah. And just all kidding aside here, I want to agree my friend Otis over there, in that you have to look at long-term in the context of the natural history of the disease. So whereas, you?re saying it?s going to be two years, three years, four years, five years, you have to recognize what the median survival is, and look at these events that Steve was talking about in relationship to that sort of a time point.

CHAIRPERSON PRZEPIORKA: Dr. Albertsen.

DR. ALBERTSEN: In terms of additional information needed, even though the FDA does not accept PSA progression as an endpoint, I would, for one, like to have seen the data presented with that as an endpoint, because one of the problems with the way that studies are currently constructed is that a valid endpoint to show efficacy is so far out in the future, that I feel as currently constructed, you have no other way of addressing the answer but saying no,

because of the way the problem is framed. Therefore, reframing the endpoint and adding some more, a two or three year follow-up I think might, in fact, lead us to a better feel for how this drug is truly working. So two pieces of information. One, a new endpoint which has not been thrown on the table yet, and a little more time.

CHAIRPERSON PRZEPIORKA: Any other comments? Okay. Now on to question two. Do the data from these trials allow for adequate definition of patient population that can be extrapolated from the non-U.S. studies to a defined group of U.S. patients who will derive significant benefit from Casodex therapy. Dr. Schoenberg.

DR. SCHOENBERG: This is ?- you?re calling for comments. Correct? I?m concerned because I think the groups of patients are very significantly not comparable. And that doesn?t mean, as I think people have noted previously, that there aren't interesting and compelling data to be derived from the European trials, but the U.S. population is very different, the one that was studied. And because of the confounding

problem of identifying exactly which pathologic entities were being studied in 24 and 25, I?m particularly concerned that we?re going to have difficulty identifying who?s going to benefit. And I am very concerned as this particularly touches upon the issue of watchful waiting, so I am very concerned about those two particular problems.

CHAIRPERSON PRZEPIORKA: Can I ask if you can give your opinion on the subgroup separately? I hear that for the localized disease group with watchful waiting you don?t believe that the subgroups, that the two groups are comparable, but what about the high risk group? Would they be more comparable, or not comparable at all?

DR. SCHOENBERG: Well, as I think we?ve discussed previously briefly, the problem, and this may be reflective of an issue, a Transatlantic practice difference, is that I think the groups that were studied in 24 and 25 are not ?- if not vanishing, substantially diminished in U.S. practice. And it?s not that those people don?t exist, but they are substantially less common. So I think yes, there are

compelling data in the higher risk groups, but again, we do have problems with definition. And I believe one of the issues we've discussed previously was the lumping of 7 with 8, 9, and 10. That is, to my mind, very problematic, so yes, I?m intrigued by that population, but I think more information will be necessary to extrapolate this to the U.S. population.

CHAIRPERSON PRZEPIORKA: Other comments? Dr. Blayney.

DR. BLAYNEY: I would take a contrary-wise point of view. I think for men who don?t want radiation, but who might have localized disease discovered at surgery, the data from 24 and 25 might be useful in helping them and their physicians make some decisions. For men who may have a very high Gleason Score of 8 or 9, who would otherwise fit ?- be much like the 24 and 25, I think in my practice in my community, that would be ?- that data would help in decision making, so I would say ?- my answer to this question would be yes.

DR. SCHOENBERG: Actually, can I just ask a question?

CHAIRPERSON PRZEPIORKA: Sure.

DR. SCHOENBERG: Could you be very specific about how it will aid in decision making? I?m just curious.

DR. BLAYNEY: Some men don?t want radiation after a positive surgical margin is discovered. Traditionally, those people are recommended, and there may be some benefit to survival to salvage radiation. If they don?t want radiation, this is an ?- I think there?s data that this treatment might be an option for them.

CHAIRPERSON PRZEPIORKA: Dr. Albertsen.

DR. ALBERTSEN: In my mind, the data from Trials 24 and 25 do provide evidence of efficacy for men with more advanced disease. The question then becomes how do you interpret advanced disease in the context of a U.S. population. Even though this wasn?t test tried, I think the physician community is treating patients with rapidly rising or high doubling time PSAs as men at high risk of failing. That probably can?t be incorporated in the labeling of this drug, but in terms of how do you do the walk across

the Atlantic. In my mind, that?s how it would be done. So, therefore, I do believe the data support efficacy in men with more advanced, or as they say, high risk disease, and I would define these, as I think people do in clinical practice, as people with rapid doubling times.

CHAIRPERSON PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: Earlier there was discussion of subset analysis and how subset analysis should be avoided. I just want to weigh in and reiterate that subset analysis really should be avoided. It is my feeling that the groups defined in 24 and 25, especially in Trial 25, can be extrapolatable, and you can find people like that in the United States. Although they are few and far between, I think you can find folks, so I ?- it might seem contrary to my first vote in the previous statements, but I do believe that you can extrapolate from the foreign trials to find similar patients in the United States.

CHAIRPERSON PRZEPIORKA: And I think like Dr. Brawley, I also believe that we?ve seen positive results here, and that there are probably patients in

the U.S. who would fit the same criteria as in the U.S. trial. Where I would disagree also is that the statistical analysis that was presented was not the most eloquent I?ve ever seen for looking for subsets of populations and risk factors for regression, and whether or not the treatment arm gives benefit, so I would disagree and say that the data as presented are probably not adequate enough to define the population very well. Other comments? Dr. George.

DR. GEORGE: There was the ?- Dr. Hoberman, if he?s still here. He is here, that he had done a number of analyses with respect to trying to adjust for factors to see if the great discrepancies between all these studies could be reconciled in certain ways; that is, to use the 24 and 25 data and see if you could predict some of the things that were observed on the 23 study. And if I?m interpreting this right, I think the answer was you couldn?t really do it. Maybe you?d like to elaborate on that a little bit.

DR. HOBERMAN: Yeah, I did it, and the numbers didn?t come out right. I was not able to close

the gap that should have been closed in the U.S. by doing that progression projection from Europe. I?m not sure exactly how this fits into the question that was being asked, but ?-

DR. GEORGE: I?m just using that as an example, and why I?m kind of reluctant in this area, because what ?- you know, if you assume ?- in general, it?s not a problem that you have studies with markedly different distributions of variables, as long as you have enough patients treated in groups that you can use statistical procedures to kind of adjust for that. In this case, it didn?t seem to work out right; that is, something wasn?t right, either the variables weren?t measured properly, the models that were being applied didn?t fit, and the European studies didn?t seem to apply to the U.S. for some reason. It would take a lot more looking at this issue to convince me that the results from 24 and 25 could be used.

CHAIRPERSON PRZEPIORKA: Dr. Redman.

DR. REDMAN: I got a little confused by Dr. Albertsen?s comments. You state that you wanted to somehow define a high risk population in a population

that wasn?t in these studies. Somebody with a doubling PSA, so nine months after they?ve had the surgery, the PSA ?- or radiation therapy, the PSA is doubling. These studies, if I?m correct, looked at you had your radiation therapy. We?re not going to wait for PSA doubling. You?re either going to go on Casodex, or you?re going to go on observation, so I don?t know how that high risk population fits into what these studies showed.

DR. ALBERTSEN: That?s why I made the comment as the way I did. When I looked at the data, the only patients that I can determine have any benefit are the ones who are high risk, i.e., the European patients, who in general have a disease that?s more advanced, precisely because they don?t do or have not been doing in 1995 aggressive PSA testing as we do in this country. So in 1995, you had a lead time introduced for most American patients which you didn?t have in Europe. And that?s why, in my mind, these two populations aren?t comparable.

When you use this drug very early on in the course of disease, it plays out over 10 or 15

years. You're not expecting, and I would be astounded to see any benefit in the first five years. Hence, if this company were to run the trial for 15 years, I think we might see a difference, so that remains to be tested. But if I had to guess one population that might be most likely to achieve, and again, this is a bit of a leap of faith, it's the very patients who we see failing radical prostatectomy or radiation therapy. And we know from the Pound data published in JAMA about two years ago, that men with PSA doubling times less than 10 months will generally progress to metastatic disease within 8 years, and will die from their disease within 13 years. But that's the time frames we play out here. And again, it's a bit of a leap of faith, but when asked the way the question was structured, if I could identify a population, considering the tools I have in 2003, that's probably the best way I could estimate such a population.

CHAIRPERSON PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: I asked a question earlier about groups of patients in the United States because we recently met with hospitals dealing with minority

populations in the New York area, and I was struck by the comment of the physicians who worked in that area, of the large number of patients that they see with prostate cancer who present with locally advanced inoperable disease because of late diagnosis. And I wondered whether or not that would not be an example of a population in the United States that was very close to the European population.

I haven't got a clue as to what those numbers are. I was wondering if our urologist did, and I gather it's hard to extrapolate those numbers. But I think there is a population in this country that doesn't get screened, that does present late, and that might well mimic the European population. It would be exactly what you'd be looking for. And they don't go on clinical trials, so there's no data for it. I actually don't think 23 applies to this question at all. Twenty-three is a different issue, totally a different study. Just because the trial was done in Europe does not mean it doesn't apply to American patients.

CHAIRPERSON PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: Yeah. David, you can perhaps correct me if I?m wrong. Grace Lu-yao showed that 30 to 40 percent of men who get radical prostatectomy in this country relapse by PSA within five years, many of them within two years. And it is now very common that those individuals get off-label LHRH agonist. I think a growing population will probably get Casodex off-label, despite what one of the advocates said a little earlier. But AstraZeneca is actually to be congratulated for doing studies looking at these populations right after initial therapy. I wish we had similar data with the other drugs that are being used in them, but one possible place for Casodex and one study that still does need to be done is in that 30 to 40 percent of Americans who after radical prostatectomy, or after ?- I don?t know the percentage after radiation therapy, who have a rising PSA. And unfortunately, that trial if it is powered for survival, is going to be a 15 year trial. But I must point out that AstraZeneca has presented data, very elegant data looking at Tamoxifen at 10 and 15 years of data, so we just need to do the equivalent

in prostate cancer. And in Tamoxifen, they show the survival benefit which may or may not be available if we use Casodex as an adjuvant.

CHAIRPERSON PRZEPIORKA: Dr. Albertsen.

DR. ALBERTSEN: Yeah. Otis, I agree with you. If I had to just pick the trial that I?d want to see today to make the decision, it?s basically men who have rising PSAs following radiation or surgery, who now face a choice, or face the problem of what do you do. What?s happening is most of them are getting LHRH agonist with the associated risks of libido, hot flashes and osteoporosis. They?d like an alternative, something that avoids those risks. However, ultimately I?m not sure which the better therapy is. What troubles me about the data is that Casodex 150 was not as good as castration in the M1 trials. Therefore, with an alternative that clearly works better in advanced stages, but it comes at a price of quality of life much earlier on. And since we?re dealing with a chronic disease, the question is what?s the appropriate choice.

The trial that needs to be done is in men

with progression following surgery or radiation. Is it best to give LHRH agonist, Casodex or placebo? I suspect no one is going to fund such a trial. It will take too long to sort out, so instead we're grappling with the data that's being handed to us.

CHAIRPERSON PRZEPIORKA: Dr. Schoenberg.

DR. SCHOENBERG: Yeah. I think this is sort of a more general comment echoing some of the things that Peter has just said. AstraZeneca, as is everyone who works on prostate cancer and works on it seriously, is to be congratulated for doing difficult trials, but the disease is what it is. And if it takes a long time to get an answer, that's the ball game. And at least from a practical clinical perspective, it's very hard to accept intermediate endpoints that have not been validated, that are of questionable value within the context of a given study. And I think one thing we need to keep in the back of our minds, probably everyone here is thinking about it, is that while it is great to offer patients choices, and all of us want to do that, I think that at some level it is unethical to represent that a

choice, any choice is a good choice. And part of our job, obviously, is to make sure that drugs that we recommend or don?t recommend get that recommendation for a reason. And I think the strength of the data here make it problematic for, at least for an American urologist like myself, to weigh in strongly and say sure, there?s clear evidence that this will be beneficial.

I think what we can say is that it may be in a very small and defined segment of a population, which really requires a much longer study, unfortunately. That?s the ball game we?re playing here.

CHAIRPERSON PRZEPIORKA: Other comments. Mr. Ohye.

MR. OHYE: I?d like to reserve a comment after the vote between this question and the next, if I may.

CHAIRPERSON PRZEPIORKA: Then I will call the question. Number two then is, do the data from Trials 24 and 25 allow for adequate definition of a patient population that can extrapolated from the non-

U.S. to the U.S. patients who will derive a significant benefit from Casodex? Dr. Albertsen.

DR. ALBERTSEN: Yes.

DR. MARTINO: Yes.

DR. PELUSI: Yes.

DR. HANNO: No.

DR. BRAWLEY: Yes.

DR. SCHOENBERG: No.

MR. ANDERSON: No.

DR. KRIST: No.

CHAIRPERSON PRZEPIORKA: No.

DR. KELSEN: Yes.

DR. REDMAN: Yes.

DR. CARPENTER: Yes.

DR. CHESON: No.

DR. GEORGE: No.

DR. BLAYNEY: Yes.

DR. REDMAN: No.

CHAIRPERSON PRZEPIORKA: I?m sorry to tell you, eight yes, eight no. Mr. Ohye, which may actually give us the deciding vote.

MR. OHYE: As you know, I?m non-voting.

However, I think the FDA in their wisdom under Subpart H in the regulations, have provided a way out for us here, because if we were to change this question to read and I?ll only refer to the last line of the question. Change it as follows, ?Define groups of U.S. patients who are likely to derive a clinical benefit from Casodex therapy?, we?re talking about using the provisions of Subpart H or accelerated approval as we did yesterday, where you have data that is likely to show, likely to provide a clinical benefit. And then we have the burden of the sponsor to show at a subsequent time, later data, could be more mature data from this study, because this is certainly not a failed study. We?re not trying to save a failed study. This was a good study. It was carried out pursuant to the agreements reached by FDA at the End of Phase 2 Meeting.

As you heard from Dr. Albertsen, we know that this drug is going to be used, available. We know the drug is going to be imported from Canada. I can go on the web site as soon as it?s available in he Canadian market. I can go on my computer and get it,

and FDA has made an announcement that they?re not going enforce importation of use of drugs for individual patients, so this cries out for, I think, the sponsor and the agency to provide adequate directions for use, and to move forward with this drug under the provisions of Subpart H. Thank you.

CHAIRPERSON PRZEPIORKA: Question three, based on the findings in Trial 23 as of June, 2000 data cut-off, it appears that Casodex does not offer a significant benefit for men with early prostate cancer who initially are treated by radical prostatectomy or radiation therapy with curative intent. In light of this observation, what population of patients, if any, who were initially treated by radical prostatectomy or radiation of curative intent in the U.S. would benefit from adjuvant therapy with Casodex? Dr. Hanno.

DR. HANNO: I don?t think it?s clear basically if any would. I don?t think we know, and we would just be guessing. And I think the key missing element in this whole discussion is, is there data that immediate hormone therapy improves survival? I mean, if it does, then a lot of this ?- then Casodex

may turn out to be a great drug. In the absence of that data from any trials on any type of hormonal therapy, we are really in the dark about this, and we?re just sort of guessing, so I would just say it?s not clear if any would.

CHAIRPERSON PRZEPIORKA: Could you just repeat then, what additional data would you require to allow you to conclude that Casodex would provide a clinically significant benefit? Part C of Question Three.

DR. HANNO: Part C of Question Three. I?d like to see either survival data, or quality of life data suggesting that early treatment in preventing the onset of metastatic lesions improves the quality of life, regardless of effects on survival, compared to treating when PSA rises or bone metastases appear. And my concern is that this indication in the U.S. for Casodex would imply that Casodex improves survival of all patients after definitive therapy. And it would become ?- there would be widespread use of adjuvant Casodex in virtually everyone who gets a radical prostatectomy or radiation therapy. And I?m not sure

that would be warranted, but I think that might well happen.

CHAIRPERSON PRZEPIORKA: Dr. Martino.

DR. MARTINO: I don?t think it?s fair to say that this trial, number 23, does not show a benefit. See, that implies that we know the future, and we don?t. The reality is that this is a trial where the relapse rate is quite small at this point in time in a patient population where that could have easily been anticipated to be the case, so the question implies that we understand that even in this population, there can never be a benefit. I think that?s an assumption on our part.

CHAIRPERSON PRZEPIORKA: And actually, if I recall the data, and I wrote it down from 23 specifically, the patients who had radiotherapy had a significant improvement or a significant lack of progression being reduced from 40 percent to 28 percent. It was the prostatectomy patients who had no benefit and no progression, as you had pointed out earlier, so I think you?re correct. And I would echo what you said about we?re not there long enough,

although the radiotherapy patients certainly look like they derive benefit. Other comments regarding 3(a)? Dr. Albertsen.

DR. ALBERTSEN: I agree with Dr. Hanno. Ultimately, the use of hormonal therapy has not yet been demonstrated to increase longevity. And the sad part is, I see any window of opportunity to prove this in a clinical trial as probably beginning to draw to a close, so I?ll address number C. Given the group of patients we know that are high risk for disease progression and death from prostate cancer, are those men with rapid PSA doubling times following a definitive therapy. That?s the population that?s key, and whether ?- and how much Casodex or any hormonal therapy alters that natural history is debatable. But that is a group that requires further study, and that?s the group that if we are extrapolating from Trial 24, you?d be extrapolating to.

CHAIRPERSON PRZEPIORKA: Other comments? So, Dr. Shames, I think the answer to ?- this was an essay question for A is, we can?t define a population based on what we have now. We would like longer

follow-up data.

Moving on to question 4 then. In the U.S. trial, Trial 23, there was no watchful waiting treatment group. (A) Has the sponsor demonstrated in trials 24 and 25 that U.S. patients with localized non-metastatic prostate cancer who are presently managed by surveillance would derive sufficient benefit from Casodex monotherapy, or immediate treatment to justify the adverse events that would be associated with such treatment? Dr. Albertsen.

DR. ALBERTSEN: I?d answer no to that.

CHAIRPERSON PRZEPIORKA: And what additional data would you require to allow you to conclude that monotherapy would provide clinically significant benefit to the U.S. patients presently managed by surveillance?

DR. ALBERTSEN: That?s defining who is getting watchful waiting in this country, because usually the persons getting watchful waiting in this country are people who are felt to be at low risk for disease progression. It?s precisely those patients that you?re going to have the least amount of efficacy

from Casodex. The ones who have a high probability of progression are the ones who might benefit, and that?s why I voted no.

CHAIRPERSON PRZEPIORKA: Would you consider patients who you are waiting and watching their PSAs rise as a potential group?

DR. ALBERTSEN: I think a potential group are those patients who elect not to have surgery or radiation, yet who have clear progression of PSA. I?m dealing with a gentleman in my community I just saw yesterday who?s been watching himself for five years. He?s 65 years old, and he just does not want to have surgery or radiation. His PSA is now up to 16. I know eventually he?s going to die from this disease. He?d be the perfect candidate to put on something like this, so I think there?s a group out there, but I think it?s small. But to a blanket statement of all patients who choose watchful waiting, that I think is inappropriate because most of the patients who choose watchful waiting are usually men in their late 70s and early 80s whose natural history is such that they are going to most likely die of a competing hazard, rather

than their prostate cancer. So, therefore, treating them with Casodex just gives them the morbidity from the treatment. It is unlikely to achieve any benefit for them.

CHAIRPERSON PRZEPIORKA: Dr. Martino.

DR. MARTINO: I guess I?m unsure now as to ?- particularly in Trial 25, the Scandinavian trial, where I thought I had seen that about 80 percent of the patients in that trial were of this population. I guess I?m not sure why it is that those patients are so different from the American population. I remember the gentleman who addressed the nature of the patients, making the statement that the patients that went into Trial 25 were men who had a time from diagnosis to entry in trial of three months, so how is that so different from what might happen in this country? I?m very confused on this patient selection issue.

CHAIRPERSON PRZEPIORKA: Dr. Albertsen.

DR. ALBERTSEN: Yeah. I think the issue has to do with PSA screening in this country. The U.S. populations were probably comparable in 1990, but

are no longer in 2003. Maybe in 2005, as the Europeans begin to more aggressively screen PSA, you?ll see a congruence. But right when this study was done in 1995, you probably had the most disparity from what was being done in this country compared to what was being done in Europe, so therefore, the pool of patients who are slated to be enrolled in Trials 24 and 25, by and large had more advanced disease than their American counterparts. So again, it goes down to the lead time associated with this disease. And if we?re talking about a lead time of at least five years, and possibly longer as a result of PSA screening, when you make a new diagnosis of someone who?s in their mid to late 70s, who has at best a 10 year survival, you could see where the benefits begin to get very marginal.

DR. MARTINO: I understand the basic concept, and I agree with the basic concept. I think what I?d like is, I?d like to hear from the PI from the Scandinavian trial that in fact, when they entered patients on this, that they really were not selected from the point of view of being diagnosed, screened

based on PSA that ?- the impression is that these were gentlemen in Europe who actually were symptomatic, and therefore, diagnosed. I?d like to know if that?s correct or not.

CHAIRPERSON PRZEPIORKA: So the question to the PI on the Scandinavian trial is, are the patients who were placed on this protocol part of the screening population, or patients who came in for a reason?

DR. IVERSEN: In response to your question, I can inform you that at that time in Scandinavia, screening with PSA was not practiced.

CHAIRPERSON PRZEPIORKA: Dr. Shoenberg.

DR. SCHOENBERG: Yeah. I mean, just as a follow-up to Dr. Albertsen?s comments, and to clarify this. There are guidelines in the U.S. for recommending watchful waiting to patients with prostate cancer. Not everybody follows them. Clinicians are accorded a relatively broad degree of latitude in advising patients about the problem, but this population is, I believe, by definition substantially different than the U.S. watchful waiting

population. Using the criteria of PSA density, the amount of biopsy material that is actually positive for carcinoma, and the Gleason Score, which by definition should be less than 6, or equivalent to 6 but not greater, so I suspect they?re really very different populations.

CHAIRPERSON PRZEPIORKA: Dr. Krist.

DR. KRIST: I agree with all the statements made. I mean, the other thing that concerns me too with the watchful waiting group is it seems like there?s a narrow window of potential benefit, where there?s a group of patients who really aren?t going to derive any benefit from treatment with Casodex, just due to the nature of their disease, and would be better off with just watchful waiting, and no therapy. And then even on the other end of the spectrum with us seeing in Trial 306 and 307, there?s the other end of the spectrum where there?s a potential group with more advanced disease who might opt for watchful waiting, who would be better off with LRHR analog, or medical castration instead.

CHAIRPERSON PRZEPIORKA: Yes.

DR. HOBERMAN: I simply have a point of information. You made a statement about in 23, radiotherapy patients having an efficacy advantage. And I?m curious where that is coming from.

CHAIRPERSON PRZEPIORKA: I copied that off an additional slide that the sponsor placed in response to a question that I had asked.

DR. HOBERMAN: Was that among the high risk group, or was that including the total sample?

CHAIRPERSON PRZEPIORKA: Just the high risk group, specifically in Trial 23.

DR. HOBERMAN: That doesn?t square.

DR. MONROE: I believe you were shown percentages, but I think the number of events were only like four total, and so you have maybe some very ?- the data by looking at percentages I don?t think are appropriately represented. I just want to bring that up, that if one looks at actual number of events, I think by looking at percentages, you get a wrong impression as to what really occurred.

CHAIRPERSON PRZEPIORKA: Thank you for clarifying that. Other comments? Dr. Shames, do you

want us to take a vote on 4(a), or what I?m hearing is that essentially we don?t believe that the patient population in 23 and 24 is something that we frequently see in the U.S., but there is a population in the U.S. who really does need to be studied, whom we would predict would have benefit from this, to answer Part C, which means another study.

DR. SHAMES: Essentially no, but we would prefer to have another study to see this. Okay. Thank you.

CHAIRPERSON PRZEPIORKA: Any other comments from the Committee? Dr. Shames, any other questions from the FDA?

DR. SHAMES: No, I appreciate this a great deal.

CHAIRPERSON PRZEPIORKA: Thank you. I call this meeting adjourned.

(Whereupon the proceedings in the above-entitled matter adjourned at 2:47 p.m.)