DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# ONCOLOGIC DRUGS ADVISORY COMMITTEE

Volume I

Tuesday, September 13, 2005

8:10 a.m.

Holiday Inn
8120 Wisconsin Avenue
Bethesda, Maryland

PARTICIPANTS

Silvana Martino, D.O., Chair
Johanna M. Clifford, M.S., RN

MEMBERS:

Ronald M. Bukowski, M.D.
Bruce D. Cheson, M.D.
Antonio J. Grillo-Lopez, M.D., Industry Representative
Pamela J. Haylock, RN, Consumer Representative
Joanne E. Mortimer, M.D.
Michael C. Perry, M.D.
Gregory H. Reaman, M.D.
Maria Rodriguez, M.D.
Alexandra M. Levine, M.D.
Maha H.A. Hussain, M.D.

CONSULTANTS (VOTING) FOR XINLAY:

Otis Brawley, M.D.
Ralph D'Agostino, Ph.D.
S. Gail Eckhardt, M.D.

PATIENT REPRESENTATIVES (VOTING):

Eugene Kazmierczak, Ph.D. (for Xinlay)

FDA STAFF:

Richard Pazdur, Ph.D.
Robert Justice, M.D.
Amna Ibrahim, M.D.
Rajeshwari Sridhara, Ph.D.
Shenghui Tang, Ph.D.

C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introduction of Committee

DR. MARTINO: I would like to call to order the proceedings of this committee. This morning the committee will discuss new drug application NDA 21-491, proposed trade name Xinlay (atrasentan hydrochloride) capsules, by Abbott Laboratories. The proposed indication is for the treatment of men with metastatic hormone-refractory prostate cancer.

We will begin by the committee members introducing themselves, and I would like to start on my left, please. You will need to push the microphone button, please.

DR. KAZMIERCZAK: Eugene Kazmierczak, patient consultant.

DR. BRAWLEY: Otis Brawley, medical oncologist and epidemiologist, from Emory University in Atlanta.

DR. D'AGOSTINO: Ralph D'Agostino, biostatistician, from Boston University.

DR. BUKOWSKI: Ron Bukowski, medical

oncologist, Cleveland Clinic.

DR. CHESON: Bruce Cheson, hematologist-oncologist, Georgetown University Hospital.

DR. ECKHARDT: Gail Eckhardt, medical oncologist at University of Colorado Cancer Center.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez, medical oncologist. I am the industry representative on this committee. However, I receive no support whatsoever from industry for being here.

DR. PERRY: Michael Perry, medical oncologist, University of Missouri, Ellis Fischel Cancer Center, Columbia, Missouri.

DR. MARTINO: Silvana Martino, medical oncology, the Angeles Clinic.

MS. CLIFFORD: Johanna Clifford, Food and Drug Administration, executive secretary to this meeting.

DR. MORTIMER: Joanne Mortimer, medical oncology, Moores University of California Sang Diego Cancer Center.

DR. LEVINE: Alexandra Levine, hematologic oncology, University of Southern California.

MS. HAYLOCK: Pamela Haylock, oncology nurse and doctoral student, University of Texas Medical Branch in Galveston.

DR. REAMAN: Gregory Reaman, pediatric oncologist, George Washington University and Children's Medical Center.

DR. TANG: Shenghui Tang, statistical reviewer for this application, FDA.

DR. SRIDHARA: Rajeshwari Sridhara statistical team leader.

DR. IBRAHIM: Amna Ibrahim, medical reviewer, FDA. DR. JUSTICE: Robert Justice, Acting Division Director, Division of Drug Oncology Products.

DR. PAZDUR: Richard Pazdur, Office Director.

DR. MARTINO: Thank you. Next Ms. Clifford will read the conflict of interest statement for the committee, please.

Conflict of Interest Statement

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. Section 208, full waivers have been granted to the following participants:

Ralph D'Agostino, Ph.D., for an unrelated advisory board activity for a competitor, for which he receives less than $10,001 per year.

Gail Eckhardt, M.D., for unrelated advisory board activities for two competitors, for which she receives less than $10,001 a year from each firm, and for unrelated consulting for a competitor, for which she receives less than

$10,0001 per year.

Ronald Bukowski, for unrelated consulting for a competitor, for which he receives less than $10,001 a year and for his employer's contract with the sponsor, funded at less than $100,000 per year.

Otis Brawley, for owning stock in a competitor, valued from $25,001 to $50,000.

Pamela Haylock for owning stock in a competitor, valued from $25,001 to $50,000.

Michael Perry, for owning stock in two competitors, valued from $5,001 to $15,000, and for owning stock in a competitor, valued less than $5,001.

A copy of the wavier statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building. We would also like to note that Dr. Antonio Grillo-Lopez is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Disease Research.

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.

DR. MARTINO: Thank you. Dr. Pazdur, would you like to make a few comments to the committee?

Opening Remarks

DR. PAZDUR: Yes. I don't have any prepared comments but Silvana asked me a question, whether this application was going to be considered for accelerated approval versus full approval. I really wanted to emphasize the reason why we are bringing this application to the committee, and that is the question is are the results that we see

in this clinical trial--do they demonstrate a persuasive, convincing effect on the endpoint that is being discussed here?

I think people have to understand that when we talk about the uncertainty with accelerated approval we are talking about the relationship between the surrogate endpoint and clinical benefit, not the therapeutic effect on that endpoint. In other words, one should have the same level of confidence and persuasiveness demonstrated on the endpoint that is under consideration. The ambiguity in relationship is between that endpoint and it being reasonably likely to predict clinical benefit, not on the therapeutic effect of that endpoint.

So, I just wanted to make that point clear, that the discussion first has to demonstrate or discuss whether we are having a persuasive, a clinically convincing effect on an endpoint. Then the discussion could go on as to whether that endpoint has clinical benefit per se or is it a surrogate reasonably likely to predict clinical

benefit--a very important distinction. Again, the level of evidence on the endpoint should be the same. You have to have convincing, persuasive findings on that endpoint.

DR. MARTINO: Thank you. At this point I would like Abbott Laboratories to present their data, and Dr. Gary Gordon will start the presentation. Doctor, can I remind you that you have until nine o'clock for your group's presentation and I do mean to keep you on time?

Abbott Laboratories Presentation

Introduction

DR. GORDON: Good morning.

[Slide]

My name is Gary Gordon. I am the divisional vice president for global oncology development at Abbott Laboratories. On behalf of Abbott Laboratories, the investigators and, most importantly, the patients who participated in the studies with atrasentan I would like to thank the FDA and the Oncology Drug Advisory Committee for allowing us to present our data to you today.

There is one correction I would like to make to the schedule. Dr. Howard Scher was scheduled to be part of the discussion this morning. He is unable to participate this morning with us because he has a conflict resulting from some of his consulting activities with FDA on related matters, and Dr. Michael Carducci will replace him.

[Slide]

The drug we are here to discuss today is atrasentan. Atrasentan is a potent and selective endothelin-1 receptor antagonist. It is an orally bioavailable drug and can be dosed once a day.

[Slide]

The disease we are here to discuss we all know about. It is prostate cancer. It is the second most common cancer in men in the United States. There will be more than 230,000 cases of prostate cancer diagnosed this year in the United States. More than 30,000 men will die of prostate cancer this year in the United States. Most of them will have advanced metastatic

hormone-refractory, metastatic prostate cancer, and 85 percent of those men will have bone metastasis and 90 percent of these men will require opiates in the last months of their life to manage pain, with 50 percent having pain requiring opiate treatment in the last three months of their life.

There are limited treatment options available for these men. You will hear more about these during the course of the presentation, but most of them are palliative with the exception of docetaxel, which was recently approved for a two-month survival benefit. However, not all patients either are eligible to receive this form of chemotherapy or choose to receive this form of chemotherapy.

[Slide]

The indication we are here to discuss today is that Xinlay, or atrasentan, is indicated for the treatment of men with hormone-refractory prostate cancer with metastasis to bone.

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The atrasentan clinical development

program began in 1996. It encompasses more than 35 clinical studies sponsored by Abbott Laboratories. These studies have included healthy normal volunteers, special populations, that is, individuals with underlying problems such as diabetic nephropathy and congestive heart failure. It has included a large number of individuals with other types of cancers but, most important for today's discussion, it has included nearly 1,200 individuals with hormone-refractory prostate cancer.

The two studies that we are here to discuss today in terms of efficacy are M96-594, which was a dose-ranging study of this drug, and M00-211, which was the pivotal trial. As you might imagine, the pivotal trial was subject to a special protocol assessment with the Food and Drug Administration prior to the enrollment of any patients. Both of these studies, the 594 study and 211 study, did have time to progression as their endpoint.

[Slide]

As you know from reading the briefing documents and from the discussions, there are some unique statistical considerations that need to be taken into account during today's discussion. Number one, study 594 and study 211 did not meet their primary endpoints. The 211 study was stopped by its data safety monitoring committee because of a recommendation that the study was going to be futile. The analysis of patients with bone metastases was not protocol-specified. So, these were all issues we will try to address during the course of today's discussion.

[Slide]

Why are we here? We are here because consistent benefit was seen in this group of men with hormone-refractory prostate cancer with metastases to bone. This group of men was identified due to the science and the analysis was driven by the science. You will hear much about that science today from Dr. Nelson. The role of the endothelin axis at the interface between prostate cancer cells and osteoblasts within the

bone micro environment over the course of this clinical development program has become increasingly understood and there has been a mutual interaction between the clinical trials and the evolution of the science.

The 211 study is a large, placebo-controlled study in men with hormone-refractory prostate cancer, and is the largest study of its type. And, 690 of the 809 patients in this study, or 85 percent, did have metastases to bone. As you will hear from other speakers and as you know, there is a large unmet need in this group of men.

[Slide]

So, the agenda for the speakers will be Dr. Joel Nelson, who will address unmet need and mechanistic rationale. Dr. Nelson is chairman of urology at the University of Pittsburgh. The efficacy discussion of the 594 study and 211 study will be presented by Dr. Darryl Sleep, from Abbott Laboratories. I will review the safety findings with you and, as I already mentioned, Dr. Michael

Carducci, who was the coordinating investigator on the 211 study will help in the discussion of where does atrasentan fit in therapy.

[Slide]

Other consultants available today to the committee and to the FDA include Dr. David Cella, professor of psychology and behavioral science, Northwestern University; Dr. David Dearnaley, professor of uro-oncology and head of urology from the Royal Marsden Hospital and Institute of Cancer Research in London; Dr. Scott Emerson, biostatistician, professor of biostatistics, from the University of Washington; Dr. Roberto Lang, professor of medicine and cardiology at the University of Chicago; and Dr. Daniel Petrylak, associate professor of medicine, Division of Hematology and Oncology at Columbia University.

[Slide]

With that, I would like to turn the podium to Dr. Nelson for a discussion of unmet need and mechanistic rationale.

Unmet Need and Mechanistic Rational

DR. NELSON: Madam Chair, members of the committee, I want to thank you for the opportunity to participate in the discussion today.

[Slide]

Dr. Gordon has already introduced to you the problem, the very large problem of prostate cancer in this country, 232,000 cases will be diagnosed this year and this will result, unfortunately, in the death of 30,000 men this year. The prevalence of the disease is also very large and men will progress in this disease to a state of hormone-refractory disease. This is defined as evidence of disease progression with castrate levels of androgen. This population of men is often treated with chemotherapy but careful analysis would indicate that only roughly half of them, in fact, will choose to be treated with chemotherapy for a variety of legitimate reasons.

[Slide]

Metastatic hormone-refractory prostate cancer is a disease in bone. As Dr. Gordon has already told you, this occurs in about 85 percent

of men who suffer from this disease, and it is classically osteoblastic, that is, an increased deposition of bone from increased activation of osteoblasts as you can see in this bone scan, the so-called super-scan, in this unfortunate man with widely metastatic bony disease.

These lesions are not inert. They involve chronic, intractable bone pain affecting about three-quarters of the patients. It leads to a major decline in their quality of life. It is the major reason in my practice why these patients require hospitalization at the end of their lives, and about 90 percent of them will, in fact, need chronic opioids to manage their pain. In this background of chronic, intractable pain are acute skeletal events which increase morbidity including pathologic fractures and spinal cord compression.

[Slide]

The treatment of this disease state is palliative. Zoledronic acid has recently been approved as an agent which can reduce skeletal-related events, but I should emphasize

that over a third of patients on this agent will continue to suffer from those events. In addition to the opioid analgesics, we will use focal radiotherapy for lesions that are symptomatic and when the disease becomes more diffuse radiopharmaceuticals will provide temporary relief. Mitoxantrone and prednisone, as you know, have also been approved as agents for palliation in this disease state.

[Slide]

What are the characteristics of the current therapies? Well, first, they are intravenous which is somewhat cumbersome and patients require admission to places where they can get an IV. They are, unfortunately, also toxic, which is one of the things we have to balance as we discuss with patients the use of these agents. For example, mitoxantrone and docetaxel, as I show here on a table which you probably can't see from the other side, clearly there is cardiovascular toxicity, dyspnea. Gastrointestinal toxicity occurs at relatively high rates and, as marrow

suppressive cytotoxic agents, we have to be aware of these. And, this is a disease with which people progress and, unfortunately, die from, so failure is inevitable. I would argue that there is a clear need for more treatment options in this disease.

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Turning to the science, the endothelins are a group of 21 amino acid peptides. Endothelin-1 was first described in 1998 and identified as the most potent vasoconstrictor known to man. There are known to be a family of endothelins, ET-1, ET-2 and ET-3. We will focus our discussion here on ET-1. These bind with differing affinities to one of two endothelin receptors, ET-A and ET-B. These are heptahelical receptors, G-protein coupled, and when ET-1 for example binds to the ET-A receptor, in addition to inducing potent vasoconstriction, depending on the cellular target, it can induce myogenesis. It can act as an antiapoptotic factor. For the sake of discussion today, it has been shown to be causal in

the osteoblastic response and, in fact, can induce pain.

[Slide]

What would be the rationale for targeting this endothelin axis in prostate cancer? Well, first, endothelin-1 is expressed in all stages of the disease, from primary prostate cancer all the way to the lethal phenotype at the time of autopsy. ET-1 clearance is reduced in hormone-refractory prostate cancer. The enzyme responsible for clearing bioactive peptides such as endothelin-1 is known as neutral endopeptidase. This is significantly reduced in its activity in men with hormone-refractory prostate cancer. Osteoblasts express endothelin-A receptors at very high density, 10 5 or 106 receptors per cell, and binding of ET-1 to those receptors increases osteoblastic proliferation, matrix deposition classically involved in the osteoblastic response. Agents such as atrasentan have been shown in preclinical models to interrupt this interaction between endothelin-1 and the ET-A receptor.

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The working hypothesis here is that prostate cancer and bone set up a reciprocal relationship where both cellular populations benefit from the presence of the other. For example, prostate cancer cells, secreting endothelin-1, activate osteoblasts which increase what they do, that is, make more new bone. As a consequence of that, growth factors in this micro environment allow prostate cancer to survive and proliferate in this micro environment.

[Slide]

Well, what is the evidence for that statement? There are several preclinical models which have elegantly demonstrated this. First, Teresa Guise and colleagues published in PNAS, which in fact made the cover of PNAS in 2003, and showed that in an animal model of osteoblastic metastases animals treated with vehicle developed osteoblastic lesions, as can be seen clearly here, in the vertebral body of this mouse, and also shown by histology with all of this new woven bone in

concert with these cancerous cells. But at both doses of atrasentan tested there was a significant reduction in new bone area and, for the sake of therapy, there was a decrease in tumor area.

[Slide]

This observation has been supported by a recent observation using a prostate cancer cell line, known LuCaP, which induces are very exuberant osteoblastic response in vehicle-treated animals. These are tumors which were implanted into the tibia of a nude mouse. You can see all of this increased new woven bone in the tibia of these animals. Again, when treated standard atrasentan there is a marked reduction in the amount of new bone that forms, certainly more than one would see with zoledronic acid treatment, and the combination of atrasentan and zoledronic acid also decreases the new bone that had been formed.

If one considers again this reciprocal relationship between new bone formation and cancer growth, you can see that there is a very large reduction in the atrasentan-treated animals in

terms of the tumor that was identified in this micro environment.

[Slide]

I have the unique perspective as one of the people initially involved in developing the hypothesis that perhaps endothelin-1 would have a role in the pathophysiology of prostate cancer when I was a fellow at Johns Hopkins, and also involved in the development of this clinical program.

In 1995 we published a paper where we identified endothelin-1 and argued that it had a role in the pathophysiology of the disease. Based on some fairly simple, straightforward experiments, we thought that perhaps the role might be that this was, in fact, the Holy Grail of hormone-refractory disease progression, a non-androgenic factor, and perhaps this was the reason why men progressed. We thought perhaps there was an inhibition of apoptosis. We proposed that there could be an osteoblastic response and, in terms of morbidity, perhaps these are agents that in fact induce pain, ET-1 induces pain.

In a really rapid fashion this was taken from the bench to the bedside. We published in '95 and Phase 1 trials were begun by Abbott Laboratories in 1996. In many ways, the clinical trial program accelerated ahead of where the preclinical models and preclinical laboratory experiments were. As we began to do increasing work in this area, it became very clear to us, as more and more evidence mounted from preclinical models, that in fact the major effect here was going to be in the bone micro environment.

As I have already told you, there was evidence published, actually after the 211 study was closed, that in fact the binding of ET-1 to the ET-A receptor was in fact causal in osteoblastic response--a clear convergence of clinical and basic science and I think a classic example of translational research.

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I would like to now invite up to the podium Dr. Darryl Sleep, who will talk to you about the efficacy of this agent. Thank you.

Efficacy

DR. SLEEP: Thank you, Dr. Nelson. Good morning. It is a pleasure for me to be here today to present the evidence for the benefit of atrasentan in men with hormone-refractory prostate cancer with metastatic disease in bone.

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We have conducted two randomized, controlled trials of atrasentan in men with hormone-refractory metastatic prostate cancer, where the primary endpoint was time to disease progression. The first was a dose-ranging study that evaluated the 10 mg dose and the 2.5 mg dose, along with placebo, in essentially asymptomatic patients. The primary endpoint was a composite of radiographic and clinical events that reflect clinical practice with this disease.

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In the primary analysis of the primary endpoint of this study in the intent-to-treat patient population there was a treatment effect in favor of atrasentan. Although this did not reach

statistical significance, there was a 23 percent reduction in risk of disease progression in this analysis, a net result which translates into almost a two-month delay in the median time to disease progression in this intent-to-treat analysis. This positive effect of atrasentan on delaying disease progression in this trial was confirmed by analysis of biomarkers of the trial. Particularly, atrasentan attenuates the rates of rise of both bone alkaline phosphatase and PSA.

[Slide]

Furthermore, there was a dose response. There was a clear greater effect with the 10 mg dose than the 2.5 mg dose, particularly in the effect on bone alkaline phosphatase. Based on the positive strong signal that we saw in this analysis of this trial, particularly with the 10 mg dose, we decided to move forward into Phase 3 trials of hormone-refractory prostate cancer with atrasentan with the 10 mg dose.

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Our pivotal study M00-211 again randomized

patients to 10 mg or placebo. An important feature of this trial that patients were to have confirmed baseline metastases based on independent review of radiographic scans collected at baseline. Patients were to be free of prostate cancer-related pain requiring opiates, and all patients were chemotherapy naive with respect to their prostate cancer therapy. Patients were well balanced between the two treatment groups, particularly with respect to those baseline characteristics that are known to have prognostic significance in this disease state.

The primary endpoint was again time to disease progression, and was also a composite of radiographic and clinical events. Patients could progress radiographically by advancement of bone scan metastases on bone scan, extra-skeletal metastases using modified RESIST criteria, or clinical progression using events that fully describe the morbidity that these patients inevitably face, including pain that requires significant, substantial intervention to control,

pathologic skeletal events, and events such as obstructed urethra requiring intervention that clearly demonstrated that the disease is progressing.

[Slide]

This was robustly defined in the protocol and the study was conducted with rigor. In fact, in consultation with the advisory boards and with the agency, all scans were scheduled every 12 weeks. There were essentially two reasons for this. The first was to avoid the potential that PSA could be influencing the time of scans and, therefore, potentially the endpoints. All patients in this trial, in fact, had scans reviewed independently by a central radiologist and all endpoints were centrally adjudicated by central oncologists to ensure consistency in the interpretation of disease progression.

[Slide]

As Dr. Gordon has already told you, in the intent-to-treat patient population this trial did not meet the primary endpoint. But what you can

see and what is most apparent in this is a very unusually shaped Kaplan-Meier curve with a clustering of events at the time of scheduled radiographic evaluations. In fact, the vast majority of patients progressed radiographically without any evidence of clinical progression using protocol-defined measures.

As you can see again in this chart, the median statistics, in other words, describing the treatment effect of atrasentan using a delay in the median time to disease progression, does not adequately represent the treatment effect of the drug because more than 50 percent of patients progressed at the first bone scan in both treatment groups. Discounting the treatment effect of atrasentan on those patients who got through the first bone scan is not an accurate description of the treatment effect of the drug. More appropriate really and more descriptive of a positive effect of atrasentan is the hazard ratio. Even in the intent-to-treat analysis there was an 11 percent or 12 percent reduction in the risk of disease

progression.

[Slide]

In the analysis of survival in the intent-to-treat population that evaluated patients initially randomized to atrasentan compared to those initially randomized to placebo there was no difference between the two treatment groups, with a median survival of approximately 20 to 20.5 months. However, this analysis is confounded by the fact that the majority of patients availed themselves of the opportunity to move into open-label atrasentan trial upon disease progression.

[Slide]

So, why are we here? What is the benefit that atrasentan provides patients with hormone-refractory prostate cancer? Well, there is clear, compelling evidence that atrasentan delays progression of disease in patients with metastatic disease in bone. This is a disease of bone. Bone metastases are responsible for the vast majority of the morbidity of the patients with this disease face. There is a clear, strong scientific

rationale to evaluate atrasentan based on the data that Dr. Nelson has presented to you showing that the endothelin axis is not only involved in the initiation but progression of bone metastases, and that atrasentan preclinically completely abrogates that treatment effect.

Furthermore, the majority of our patients, consistent with what we know about the disease, have metastatic disease in their bone confirmed at baseline by independent review of radiological scans, 690 out or the 809 patients. We, therefore, conducted an analysis on the treatment effect of atrasentan in patients with confirmed baseline bone metastases at the time that the study blind was broken.

In the primary analysis of this patient population of the primary protocol-specified disease progression endpoint, there was a treatment effect in favor of atrasentan in patients with metastatic disease in their bone. There was a 19 percent reduction in the risk of disease progression in this patient population. The

positive effect of atrasentan on delaying disease progression, as determined by the primary endpoint, was confirmed by a number of analyses of other protocol-specified secondary endpoints that have been included in the briefing document.

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I would like to focus now on essentially three of those. The first two reflect other markers of progression of the disease and, importantly, patient-reported outcomes of quality of life.

[Slide]

Firstly, bone alkaline phosphatase rises relentlessly in patients with hormone-refractory metastatic prostate cancer representing tumor burden and progression of disease within bone. Atrasentan significantly attenuates the rate of rise of bone alkaline phosphatase at each time point in this analysis.

[Slide]

Similarly with PSA, PSA is a recognized marker of tumor progression and tumor burden in

prostate cancer. Atrasentan, again, significantly attenuated the rise of PSA compared to placebo in patients with bone metastases.

[Slide]

These analyses confirm that atrasentan delays the progression of this disease in patients with metastatic disease to bone.

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Turning now to patient-reported outcomes of quality of life, we used two instruments in this trial to define patient-reported allopurinol, the FACT-P and the EORTC, both validated questionnaires evaluating quality of life. FACT-P in particular comprises a general quality of life outcome measure which measures things such as functional well being, emotional well being but, importantly, includes an independently validated disease-specific measure, the prostate cancer subscore. In an analysis of quality of life there was a consistent treatment effect in favor of atrasentan showing a quality of life benefit particularly in the prostate cancer subscore.

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If we look at this in a little bit more detail, using this disease-specific measure of quality of life you can see that quality of life deteriorates rapidly in patients with hormone-refractory prostate cancer, particularly metastatic to bone. On the other hand, patients receiving atrasentan had a significant delay in the deterioration associated with this disease, with a significant improvement relative to placebo at each time point in this analysis.

[Slide]

In order to determine the treatment effect and the magnitude of the delay in quality of life, we conducted an exploratory analysis looking at time to a 50 percent deterioration in the pain component of the prostate cancer subscore. This analysis shows that patients receiving atrasentan have a greater than two-month delay in the quality of life deterioration associated with this disease.

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I would now like to review the aggregate

data that supports the benefit of atrasentan in men with hormone-refractory prostate cancer with metastatic disease in bone. The first and the most important of these is that atrasentan in this patient population significantly delays disease progression, which was the protocol-specified primary endpoint of the study, with a 19 percent reduction in the risk of disease progression. Furthermore, there was a positive effect on both the radiographic and the clinical components of this disease progression endpoint.

[Slide]

This was supported by the analysis of the protocol-specified endpoints measuring disease progression on biomarkers, with a significant attenuation of both bone alkaline phosphatase and PSA, confirming that atrasentan delays progression of the disease.

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But most important, this translates into meaningful, relevant and significant benefit for patients with the disease, particularly as measured

by the protocol-specified prostate cancer subscore of the FACT-P, with an almost two-month delay in disease progression and an exploratory analysis, again included in the briefing document, showing that an 85-day delay in the time to the initiation of the first opiate analgesia and a 40-day delay in the time to the manifestation of the first event of bone pain reported as an adverse event.

[Slide]

These positive results in study 211 are confirmed by analyses of the same endpoints in study 594 in patients with confirmed abnormal bone scans at baseline. The results, particularly with respect to the point estimates, all show a directionally similar trend in study 594 compared to study 211, showing consistency of the treatment effect across two studies.

So, in conclusion, these data that I have presented to you today provide compelling evidence that patients with hormone-refractory metastatic prostate cancer with metastases to bone will derive significant benefit from treatment with atrasentan.

[Slide]

Thank you for your attention and I would now like to hand over the podium to my colleague, Dr. Gary Gordon, to describe the safety experience with atrasentan.

Safety

DR. GORDON: I am Gary Gordon and what I would like to do is review with you the safety experience in the Phase 2/3 studies with atrasentan.

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As I already mentioned, Abbott has conducted more than 35 sponsored studies that involve nearly 1,700 individuals including healthy volunteers, special populations and individuals with prostate cancer. There are over 1,100 prostate cancer patients who have received atrasentan and 676 of these individuals have participated in Phase 2/3 placebo-controlled studies, and it is this group of individuals that form the comparative safety database that I am going to discuss.

The long-term exposure within this group is 270 days and 584 individuals were treated for greater than six months, and nearly 300 were treated for longer than a year.

[Slide]

As you have heard, atrasentan is a targeted and potent endothelin-A receptor antagonist. As one would expect from this class of drugs, it causes vasodilation and fluid retention. Many of the events and most of the side effects that we have seen in the trial are potentially related to this mechanism. Most of the adverse events in this trial were mild. Most resolved either spontaneously or with treatment.

[Slide]

What I would like to do first is review the overall Phase 2/3 experience in terms of adverse events. The total number of adverse events in this trial in all treatment groups was high, with 98 percent of the individuals in the atrasentan 10 mg group having some adverse event and 96 percent of those individuals in the placebo

group having an adverse event.

If one focuses on grade 3/4 severe adverse events, serious adverse events and discontinuations due to adverse events, the rates are similar between the two groups. Importantly, if one focuses on deaths due to adverse events, again, there are 6 percent, or 31 individuals in the atrasentan 10 mg group and 28 individuals, or 5 percent, in the placebo group.

[Slide]

Turning to a discussion of the statistically significant adverse events occurring in 10 percent or greater of any treatment group, the first thing that is immediately apparent is that bone pain, as one would expect in this patient population, is an exceedingly common adverse event and, in fact, is more common in the placebo patients at any grade and, importantly, in grade 3/4 events, and the difference is statistically significant between placebo and atrasentan.

Turning to other events such as peripheral edema, rhinitis, headache, anemia, infection and

dyspnea, one can see that numerically any grade event is more common in individuals receiving atrasentan at 10 mg. Focusing, however, on the 10 mg dose, peripheral edema, for instance, occurs in seven individuals in the atrasentan patient population, virtually identical to the placebo population, suggesting that all peripheral edema, for instance, does not suggest congestive heart failure. Again, for most of these events the results are quite similar between the two groups when one focuses on grade 3/4 events.

[Slide]

Given the class of drug that we are dealing with, a drug that causes vasodilation and fluid retention, as common with other drugs in this class, we thought it would be important to focus on certain types of cardiovascular events. This included arrhythmias, heart failure and myocardial infarction.

In the case of heart failure and myocardial infarction, an independent adjudication process was employed to be sure that we captured

accurately all events as reported by investigators. For the adjudication of heart failure Dr. John Teerlink, who is an associate professor of medicine from the University of California and the Director of the Heart Failure Clinic at the Veterans Affairs Medical Center, as well as a member of the FDA Cardiovascular and Renal Drugs Advisory Committee, led that adjudication process. He is not able to be here today because he is a government employee. In terms of myocardial infarction, Dr. Teerlink and Dr. Michael Parmacek, who is Chief of the Division of Cardiovascular Medicine at the University of Pennsylvania, were involved in the adjudication processes.

[Slide]

Turning to arrhythmias, we can summarize this by saying that based on our preclinical experience we did not expect to see arrhythmias as none were seen in a variety of preclinical models. As I will show you shortly, there were few grade 3/4 events and no deaths resulted from arrhythmia.

[Slide]

This is highlighted on this slide. If one focuses on grade 3/4 events, you can see that for a wide variety of events there are virtually no differences between atrasentan and placebo.

[Slide]

Turning to heart failure, there were more individuals in the atrasentan 10 mg group who did experience heart failure compared to placebo, with the rates being 4 percent in the atrasentan group and 1 percent in the placebo group. This was true regardless of whether one looked at the 1.5 mg dose of atrasentan from the Phase 2 studies, the dose-ranging study, or the 10 mg dose from Phase 2/3 studies. This numerical increase, in fact, does carry through grade 3/4 events, study discontinuations and deaths, with seven deaths in the atrasentan group and one in the placebo group.

I will point out that the adjudication process indicated that the investigators did do a very good job of identifying congestive heart failure and, in fact, did not identify additional cases or change the rates within this category.

[Slide]

But what I would like to do is turn to discussion of the resolution of cases of congestive heart failure. If one looks at the 28 cases putting together the 2.5 mg group and the 10 mg group, of the 28 individuals who experienced heart failure, 18 of these resolved. Ten individuals resolved either while continuing atrasentan therapy or having atrasentan therapy discontinued, having their disease stabilized and then re-instituting treatment with atrasentan. Eight individuals resolved and chose not to continue treatment with atrasentan. Three individuals had not resolved as of the date of their last follow-up. There were seven deaths attributed by the investigators to heart failure. The adjudication process showed that four of these events were, in fact, cardiovascular related, with two of them being events preceded by an MI. So, there was an antecedent MI prior to the development of heart failure and this happened in two individuals who discontinued beta-blockers without medical

supervision. Three of the deaths were adjudicated as being due to prostate cancer, and these were deaths that the investigators had indicated both prostate cancer and congestive heart failure as possible causes of death and upon adjudication there was minimal evidence of heart failure, or no evidence of heart failure at the time of death.

[Slide]

The last event I want to discuss with you is myocardial infarction. Myocardial infarction was more common in the 10 mg treatment group than it was in the placebo group, with nine events in the atrasentan group and two in the placebo group. As you would expect, most of these events were grade 3/4 events and some did result in study discontinuation. Unfortunately, three individuals did die of myocardial infarction, two in the atrasentan group and one in the placebo group, suggesting that there is not a major difference of mortality due to myocardial infarction in individuals treated with atrasentan.

Given the fact that these were large

studies, conducted over multiple sites, it was important for us, once we were able to aggregate the data and have the independent adjudicators review these cases when, in fact, an additional case was identified, to ask the question could we learn something about who are the individuals likely to experience this event.

[Slide]

Upon review of those cases, it turns out that eight of the ten individuals who experienced a myocardial infarction had an underlying history of ischemic heart disease. Seven of the ten individuals had one or more preceding event. This included one individual who had atrasentan therapy started while experiencing unstable angina; three who developed angina after starting the drug and several days prior to having a myocardial infarction; two patients who stopped beta-blockers prior to experiencing the MI; and four individuals who were noted shortly before their myocardial infarction to have hemoglobins of less than 10, suggesting that there are characteristics or signs

and symptoms that one should be aware of in taking care of these patients.

[Slide]

So, let me just summarize briefly our experience with cardiovascular events: Arrhythmias, few grade 3/4 events, no deaths. Heart failure and myocardial infarction, a rigorous adjudication process to be sure that there was no under-reporting of events and that was the case. Many of these events are manageable and there are identifiable risk factors for these individuals.

[Slide]

Broadly, there are cardiovascular safety recommendations for the use of this drug in these individuals. As with any other vasoactive compounds you would use in a group of older men with underlying disease, particularly underlying cancer, one would want to carefully consider the cardiovascular risk factors prior to initiating any therapy with a vasoactive compound. Physicians need to carefully monitor these patients who are at risk and patients need to be sure that they report

signs and symptoms to their physicians. When these are observed or identified treatment needs to be initiated, particularly in terms of volume overload and heart failure.

[Slide]

In summary, the safety experience with atrasentan is large and based on a fairly large safety database. The overall safety profile when one considers grade 3/4 events, discontinuations and deaths is similar between placebo and atrasentan. Serious cardiovascular events are infrequent and with monitoring can be managed. In data that I haven't shown but which was in the briefing document, no significant drug interactions warranting dose adjustment were observed either in these studies or in specific drug interaction studies, and no significant hepatic, renal or marrow toxicities were noted.

[Slide]

What I would like to do now is turn the podium to Dr. Michael Carducci who will, again, have a discussion of the role in therapy for

atrasentan.

Places in Therapy

DR. CARDUCCI: Thank you, Gary. Good morning. My name is Mike Carducci, co-leader of the prostate cancer program and director of translational drug development of the Kimmel Cancer Center at Johns Hopkins. I have been involved in prostate cancer research for many years and have been actively involved in the development of atrasentan since its inception in 1995. I am very pleased to be here this morning to help with today's discussion of atrasentan.

[Slide]

Eighty-five percent of men with hormone-refractory prostate cancer develop bone metastasis. These men face an unenviable future. They are almost certain to die of the disease which too often is preceded by the development of pain from their bone metastasis. This pain is debilitating and difficult to control even with opioid analgesics. Both the disease itself and the treatments available to try and control it can

reduce the quality of life for these individuals.

This slide illustrates the disease continuum for men with hormone-refractory disease and bone metastasis. As shown, some are symptomatic and some are not. But most men without symptoms will develop them in the future. The men we are discussing today are those with documented metastasis to bone with no symptoms, who are hoping to delay not only death from their disease but progression to the point where symptoms compromise their overall well being.

[Slide]

I would like to describe the options for men with hormone-refractory disease and bone metastasis who have or do not have symptoms related to these metastases. Consider the patient with symptoms. Analgesics, both non-opioid and opioid, may relieve symptoms but do not treat the disease itself. Radiation therapy is useful if a single painful area can be identified but in most cases the spread is diffuse. Bisphosphonates can delay events but have no direct anti-tumor effects and do

not affect PSA. Radiopharmaceuticals are used predominantly in men with severe pain and in them they compromise a bone marrow that is already compromised by the tumor. Chemotherapy, intravenous mitoxantrone provides palliation of pain. Docetaxel can relieve symptoms and prolong life but at the cost of a significant treatment burden to these patients and it is not curative. Therefore, the timing of docetaxel use remains controversial. Moreover, most of these therapies require parenteral administration.

[Slide]

For patients who have no symptoms from their bone metastases, those in the studies that were presented today, the choices are also limited. In some cases second- and third-line hormonal therapies are used and in others docetaxel is recommended. But once again, the patient with symptoms is not always ready for chemotherapy, recognizing the treatment burden and the fact that chemotherapy is not curative. Clearly, more options are needed, particularly those that are

directed to the underlying mechanisms that contribute to cancer growth in the bone and the response of the bone to cancer.

[Slide]

Let me illustrate the clinical scenario in a different way and perhaps personalize it with the issue that a patient of mine with asymptomatic hormone-refractory bone metastasis is faced with. This slide illustrates sequential bone scans over a one-year interval in a 68 year-old engineer with progressive hormone-refractory bone metastasis.

The first scan was taken after his initial response to hormonal therapy at a time when his PSA was rising. He was treated with a variety of hormones and with bisphosphonates but despite this his disease continued to progress.

He asks about his options, worried that he could develop pain from his disease at any time while recognizing that at the present time he has no symptoms. He wishes to spend his winter in Florida to avoid frequent hospital clinic visits and continue to be symptom-free for as long as

possible. So, what are his choices? Should we radiate the shoulder? Should we give him radiopharmaceuticals or start chemotherapy?

[Slide]

So, what is this dilemma? His PSA is going up; his bone scan is getting worse; he knows his disease is progressing and that he is at risk of dying of this disease. In addition, he knows that pain will ultimately require opioids. As such, he is at risk for significant morbidity from both the metastasis, that is, pain and spinal cord compression, as well as the side effects of the medications needed to control the disease morbidity, both of which result in loss of mobility, fatigue, constipation, weight loss and overall deterioration in quality of life, just to name a few.

[Slide]

To restate, the clinical dilemma facing both the patient and his physician is how can we maintain his quality of life for as long as possible? His questions for me are, are there

options before I start chemotherapy, ones that are more convenient and that will delay disease progression?

[Slide]

As his physician, I would be particularly interested in a drug that targets the signals between the prostate cancer cell and the bone and the response of the bone and the tumor. Atrasentan blocks endothelin-1, a signal that is causal in the osteoblastic bone response to the tumor. Atrasentan, therefore, interrupts the vicious cycle that leads to progression of this disease.

[Slide]

As you have heard today, atrasentan is an option for the patient with progressive disease in bone who has no symptoms. Atrasentan can delay the time to progression as measured by bone scan progression and the development of clinical events. Consistent with these results was the documented observation that the biomarkers of bone progression were also improved and there was an effect on PSA as well.

The clinical effects demonstrating benefit include delay in the decline in the FACT-P score and the need for opioids to control cancer-related pain. All of the results are consistent with the fundamental discoveries of the mechanism of action of atrasentan as related to the pathogenesis of prostate cancer and bone metastasis. The results were generated following a preliminary study showing similar effects.

[Slide]

So, in summary, atrasentan, the drug being reviewed today, is a novel targeted therapy for the 85 percent of men with hormone-refractory prostate cancer who have developed bone metastasis. The proposed use was identified from fundamental scientific discoveries on the mechanism of action of the drug. It has been extensively evaluated in two double-blind, placebo-controlled trials and the results observed were consistent with the mechanism.

Patients who may benefit can be easily identified. For them atrasentan offers a unique

option, filling an unmet need to further delay the development of bone-related complications with convenient, once-daily outpatient dosing. As PI of the Phase 3 study and having treated over 95 patients myself over the years with atrasentan, I can say that the potential toxicities are predictable and manageable. It is my opinion that atrasentan should be made available for use so that there are more options to delay disease progression and maintain quality of life, that is, something to give us more good days. Thank you.

DR. MARTINO: Thank you. Next I would like to turn to the FDA for their presentation, please. Dr. Ibrahim is up first.

FDA Presentation

Clinical Review

DR. IBRAHIM: Good morning. I am Amna Ibrahim. Together with Dr. Shenghui Tang, I will discuss with you the findings of the FDA review of the two clinical studies of atrasentan in men with metastatic hormone-refractory prostate cancer.

You have already seen the study designs

and I will only briefly touch on them. In addition to the results of the study, we will address a few subgroup analyses submitted in the NDA. The major issues are is there convincing evidence of efficacy of atrasentan? If there is, is the risk/benefit ratio acceptable for the approval of atrasentan?

[Slide]

We will first present the past approvals of the hormone-refractory prostate cancer, their endpoints and bases of approval; then the Phase 3 study design and the prespecified endpoints; results of the primary endpoint, which was time to disease progression. The secondary and some tertiary endpoints will be presented. Some of the subgroup analyses submitted by Abbott will be discussed. Reliability and relevance of the results of the primary endpoint in the Phase 3 trial will also be discussed.

The Phase 2 studies are not acceptable for approval based on its design, conduct and results, and these will be presented only briefly. Some safety concerns have been observed in the

atrasentan studies. The pertinent safety concerns from the Phase 3 study will be presented and Phase 2 study results will be used for corroboration.

[Slide]

In recent years there have been two approvals for men with hormone-refractory prostate cancer. The first approval was based on a study that evaluated a combination of mitoxantrone with prednisone versus prednisone alone. An improvement in the prespecified primary endpoint of decrease in pain on a six-point scale was demonstrated. An interpretable pain scale analysis was used that measured the intensity of pain. A minimum of six weeks of improvement was required, and this was supported by improvement in time to progression.

The basis of approval of Taxotere in combination with prednisone was improvement in overall survival and this was over an active control of mitoxantrone and prednisone. Approval of both these drugs was based on improvement in prespecified endpoints. The results of these studies are clinically and statistically

persuasive.

[Slide]

As you already know, the Phase 3 study was a randomized, double-blind study with two arms, atrasentan 10 mg and placebo. The analyses were mostly based on a central independent review blinded to PSA values. The investigator bias due to PSA changes were prevented.

It is to be noted that quality of life endpoints were not included in the primary or secondary endpoints and, as Dr. Tang, the statistics reviewer, will tell you, the protocol specified that no claims would be made based on the results of the tertiary endpoints. A detailed analysis plan was not included for quality of life analyses. Pain was not a prespecified primary, secondary or tertiary endpoint.

[Slide]

The protocol-specified primary endpoint, time to disease progression, is defined as the time from randomization to the first event of disease progression. Disease progression was a composite

of four main classes that you see on the slide. Radiographic progressions were evaluated by bone scans for skeletal mets and CT scans for soft tissue mets, and were repeated every three months. CT scans were repeated after baseline only if soft tissue mets were observed. Interventions for pain could be one of many, such as chemotherapy and radiation. However, in most cases this meant use of opioids. Intervention for prostate cancer complications and skeletal-related events were also included in disease progression events.

[Slide]

Radiographic events drove the results of the study. Of all progression events, 74 percent of the events were those of radiographic progression. Pain-related events were 20 percent and interventions for prostate cancer and SREs together constituted 5 percent events.

The table presents another view of the same results in the two arms of the study. It gives the percentage of patients with any event and 77 percent of patients on the placebo arm had an

event versus 73 percent on the atrasentan arm, as you will see in the last column on the right. The percentages in the table have the number of intent-to-treat population as the denominator. The difference in the percentages of events was not statistically significant. As can be observed from the table, the percentages of patients in the four event groups were similar on both arms.

[Slide]

Atrasentan failed the primary endpoint of time to disease progression in the intent-to-treat population. It failed four of five secondary endpoints. The failed secondary endpoints were overall survival, time to PSA progression, and change in bone scan index. Progression-free survival was a co-primary endpoint for the European regulatory agency and is being treated as a secondary endpoint. This too failed.

The only secondary endpoint that was statistically significant was a mean change in bone alkaline phosphatase from baseline. However, a mean difference of 20 ng/ml in bone alkaline

phosphatase is of questionable clinical significance and benefit to the patient.

There were many prespecified tertiary endpoints. Many of these failed. These failed tertiary endpoints included quality of life, adjusted time to disease progression, Karnofsky performance status and mean change in PSA.

[Slide]

The other major study that was submitted was a three-arm randomized Phase 2 study. The three arms of the study were placebo, atrasentan 2.5 mg and atrasentan 10 mg. This study was markedly different from the Phase 3 study and I will point out these differences to you.

The population in the Phase 3 study did not have prior therapy other than the hormones. Over 60 percent of patients in the Phase 2 study had received prior therapies other than hormones. Prior therapies include surgery, radiation, steroids, radiopharmaceuticals, biologic therapy and other treatments.

The patients on the placebo arm were more

heavily pretreated. For example, 25 percent of patients on the placebo arm had received prior chemotherapy and 18 percent on the atrasentan 10 mg had received chemotherapy. Patients with prostate cancer pain were not excluded from the Phase 2 study, unlike those in the Phase 3 study. The primary endpoint was time to disease progression but the definition was different from that in the Phase 3 study.

[Slide]

The events defining disease progression in the Phase 2 study are given in this slide. Many of them are vague. Symptoms do not require objective proof of disease progression. Pain was evaluated inadequately and was defined differently from the Phase 3 study. There was no required duration of opioids and no required evidence of prostate cancer at the site of pain as in the Phase 3 study. Many of the investigator-defined measures, such as weakness or deterioration, could be age related or due to other co-morbid conditions. Lastly, there is no standard way to measure a PSA rise. This is

not an acceptable regulatory endpoint at this time.

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Greater than 50 percent protocol violations on the atrasentan arm, as assessed by the applicant, reflect on the conduct of the Phase 2 study. This Phase 2 study also failed its primary endpoint of time to disease progression in the intent-to-treat population.

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I will now ask Dr. Tang, our statistics reviewer, to discuss the statistical aspects of the atrasentan efficacy. I will continue the clinical presentation after his presentation.

Statistical Review

DR. TANG: Thank you, Dr. Ibrahim. Good morning. I am Shenghui Tang.

[Slide]

This slide presents an outline of my presentation. There are several major statistical problems with this application, as listed here. First, early closure of the Phase 3 study for lack of efficacy. Second, both the Phase 3 and the

Phase 2 trials failed to demonstrate efficacy based on the primary endpoint. Third, this NDA submission is based primarily on post hoc analyses of subgroups, pooled analyses of trials with different designs and endpoint measures and pain analyses that were not prespecified. Finally, the claims in this submission are based on many analyses without adequate adjustment for multiple comparisons.

[Slide]

In September, 2002 the independent data monitoring committee of the Phase 3 study conducted an efficacy analysis of time to disease progression based on 343 progression events from the 809 patients. This analysis showed no benefit from atrasentan compared to placebo, and the independent committee recommended closure of further accrual. The applicant closed the study in March, 2003. The current application is based on updated data on these 809 patients.

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Dr. Ibrahim described the time to disease

progression primary endpoint of the Phase 3 atrasentan study and the Phase 2 study. This slide summarizes the primary efficacy analyses. As highlighted here, the primary analyses in both Phase 3 and Phase 2 studies failed to demonstrate delay in disease progression in the atrasentan treatment group with p values greater than 0.05. The protocol-specified weighted test also did not show a significant difference.

[Slide]

The failed primary endpoint analysis used all of the two-sided alpha of 0.05 and p values from further testing cannot be compared to 0.05 to declare significance. Any further analyses can only inflate the false-positive rate.

[Slide]

The applicant submitted the four secondary analyses based on the Phase 3 trial. Three of these analyses are not statistically significant. Specifically, there was no significant improvement in survival with atrasentan compared to placebo or sugar pill. Only change an ALP had a nominal p

value of 0.001. However, this was not adjusted for multiple testing and not all patients are included in this ALP analysis.

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Furthermore, it is important to note that the applicant had clearly specified in the protocol that if the primary efficacy analysis is not statistically significant at the alpha level of 0.05, then statistically significance will not be declared for any of the secondary analyses, regardless of the observed p values. Therefore, with the failed primary analysis all prespecified secondary and tertiary analyses should be considered as exploratory.

[Slide]

With the failed primary analysis, the sponsor submitted the following subgroup analyses in the Phase 3 trial. The subgroup analyses on a per-protocol patient population were submitted at the time of the NDA submission. The subgroup analyses with bone metastases at baseline were also submitted at the time of the NDA submission.

Within this subgroup a new analysis of clinical disease progression was reported for the first time in the briefing document. The per-protocol population includes 87 percent of the overall patient population. The definition of the per-protocol population was detailed in the study review of the briefing package.

[Slide]

Here are the results from the per-protocol analysis and the analysis of patients with bone metastases at baseline. These two analyses are not adjusted for multiple comparisons, therefore, the nominal p values are not presented here. The p values are not interpretable due to the failed primary analysis and cannot be compared to the 0.05 level.

[Slide]

The Phase 3 study was designed to answer questions about the atrasentan effect in the entire population, not answer the question about subgroups. Although the per-protocol analysis was outlined in the protocol, it was considered as a

tertiary analysis in the protocol. The protocol also clearly stated that significance would not be declared for per-protocol analysis regardless of the observed p values. After the study failed to demonstrate efficacy, the applicant submitted subgroup analyses in patients with bone metastases at baseline to support an indication for this subgroup of patients.

[Slide]

The analysis of time to disease progression due to a clinical event was reported in the applicant's briefing package, again, after the study failed to demonstrate efficacy and after the NDA was submitted to FDA. The applicant submitted this analysis for the first time in the briefing document to support the efficacy of atrasentan. FDA has the following concerns with this analysis:

[Slide]

First, it was not prespecified. It is a post hoc analysis without any adjustment for multiple comparisons. p values from this analysis are not interpretable, that is, it cannot be

compared to the 0.05 level. Also, in this analysis the applicant has censored all radiological progressions, that is, counting these progressions as no events. In other words, this analysis includes 75 percent informed censoring. This analysis is not acceptable for confirmatory evidence and can only be considered as exploratory.

[Slide]

A major concern with many of the analyses submitted to support approval of atrasentan is that these analyses violate well-established standards for statistical analyses of clinical trials. International standards, as outlined in the International Conference on Harmonization, E9 Guidelines state that adjustment should always be considered and the details of any adjustment procedure should be set out in the analysis plan. These guidelines also state that in most cases, subgroup and interaction analyses are exploratory and should be clearly identified as such. They should explore the uniformity of any treatment effects found overall.

[Slide]

Furthermore, the ICH E3 guidelines state that these analyses are not intended to salvage an otherwise non-supportive study but may suggest hypotheses worth examining in other studies or be helpful in refining labeling information, patient selection, dose selection, etc.

[Slide]

FDA has a number of concerns with these subgroup analyses. Subgroup analyses increase the likelihood of false conclusions because they have high false-positive or false-negative rates. For statistical results from analyses that are not anticipated or not adequately described an analysis plan must be interpreted with extreme caution because false-positive findings increase as the number of significant tests performed increases.

In the case of atrasentan, the p values from any subgroup analyses are not interpretable because the primary analysis failed. Post hoc analyses such as these subgroup analyses are exploratory analyses, useful for hypothesis

generating, not for hypothesis testing. For these reasons, FDA considers the findings from subgroup analyses inadequate evidence of efficacy on their own. These findings need to be confirmed through future well-controlled study.

[Slide]

The applicant submitted a pooled time to disease progression analysis by combining data from the two studies. This analysis included about 1,000 patients. The pooled analysis is not acceptable because of many reasons, including the following reasons: Neither trial individually shows a statistically significant difference. Both studies had different definitions for the primary endpoint of time to disease progression, as discussed here by Dr. Ibrahim. The Phase 2 and the Phase 3 studies had different eligibility criteria and accrued different patient populations. Atrasentan formulations used in these two studies are not bioequivalent.

[Slide]

The proposed analysis for pooling trials

together is a post hoc analysis. Unlike the Phase 3 study, no independent review of progression evaluation was conducted in the Phase 2 study. Pooling data causes imbalance in randomization. Of note, the Phase 2 study was a three-arm study and the Phase 3 study was a two-arm study. Finally, the type 1 error is not controlled.

[Slide]

In the protocol quality of life analysis was defined as a tertiary endpoint analysis. The protocol statistical analysis plan was never meant to include the QoL as a primary efficacy analysis. QoL was measured using two instruments, the Functional Assessment Cancer Therapy-Prostate and the European Organization for Research and Treatment of Cancer quality of life questionnaire. The protocol did not specify the statistical hypothesis for QoL analysis. No statistical adjustment was made for the multiple comparisons and the multiple scores tested.

[Slide]

The applicant reported eight comparisons

in mean change from baseline to final assessment for FACT-P and the subscores. None of them had a p value less than 0.05 except for the prostate cancer subscore, as circled in this slide. The results using the EORTC instrument also did not show significant change in mean scores.

[Slide]

The total questions in the prostate cancer subscore of the FACT-P instrument are listed in this slide. These include functional and pain-related items. Each item on this subscale was scored from 0-4. So, a total score could range from 0-48.

[Slide]

With the PCS scores ranging from a possible 0-48, it is difficult to interpret the observed PCS mean change of 1.02 and the clinical meaning of such a change on a scale of 0-48. Both QoL instruments ask the patients to rate symptoms based on their experience over a seven-day recall period and that is likely to have a recall bias. The PCS score cannot support a conclusion of

improved QoL because it does not capture all the patient perceived impact of atrasentan treatment. Many of the observed adverse events are not captured by the PCS. Finally, due to the missing values, this analysis was not based on all the randomized population.

[Slide]

The applicant submitted analyses comparing mean change in pain-related scores in the prostate cancer subscale with the NDA. Now, for the first time, the sponsor has reanalyzed and reported time to 50 percent deterioration in pain-related scores in their briefing document.

[Slide]

Of the total questions in the prostate cancer subscale, or PCS, presented previously there are four pain-related questions, shown in this slide. They are: I have aches and pain that bother me. I have certain areas of my body where I experience significant pain. My pain keeps me from doing things I want to do. I am satisfied with my present comfort level. None of these four

pain-related questions are specific to bone pain. Pain may not reflect the pain due to the prostate cancer. For example, we know that arthritis pain is a major cause of pain in older patients. Also, these questions do not measure the severity of pain. Each of these are scored on a scale of 0-4 and the total score could range from 0-16.

[Slide]

The pain-related questions from PCS are not adequate to support a conclusion about the impact of atrasentan pain because the measure was not designed or validated for such use. With the PCS pain scores ranging from a possible 0-16, it is difficult to interpret the clinical significance of the observed PCS pain score mean change of 0.7, which is less than 1.0. Each pain item measures a different attribute of pain with the seven-day recall period, which could potentially introduce a recall bias. None of the four pain-related questions are specific to bone pain.

[Slide]

The analysis of time to 50 percent

deterioration in FACT-P and pain-related QoL scores was reported in the applicant's briefing document. Again, the applicant submitted this analysis for the first time in their briefing package to support the efficacy of atrasentan after the study failed to demonstrate efficacy and after the NDA was submitted to FDA. This analysis is not acceptable.

First, it was not prespecified. It is a post hoc analysis without any adjustment for multiple comparisons. p values from this analysis are not interpretable and cannot be compared to 0.05.

Furthermore, of the total 690 patients with bone metastases at baseline, as reported by the sponsor, only 626 patients, or 90 percent of patients, had a pain score at time zero; by 100 days less than half of the patients in this analysis. In all, more than 70 percent of patients are censored for this analysis. This analysis is not acceptable.

I have presented to you only a few of numerous analyses submitted by the sponsor after

they knew that the study had failed. There has been no type 1 error adjustment for these multiple analyses. In summary, atrasentan is not superior to placebo with respect to time to disease progression or quality of life as measured in this study or overall survival. Any conclusions of treatment efficacy based solely on exploratory subgroup analyses are not acceptable. Thank you for your attention. Dr. Ibrahim will now continue the presentation.

Clinical Review Continued

DR. IBRAHIM: Thank you, Dr. Tang.

[Slide]

I will now discuss the clinical relevance and reliability of the results of time to disease progression, clinical aspects of post hoc subgroup analyses and safety of atrasentan.

[Slide]

Hazard ratios give only an incomplete picture. Hazard ratios may represent statistical significance, however, clinical relevance as the benefit provided to the patient is not captured.

For example, hazard ratios will treat the improvement from three days to six days the same as improvement from three years to six years. The same is true for proportional or any other ratio that may have been described.

We will see in the next slide that there is a difference of only a few days in time to disease progression when comparing atrasentan and placebo whether it is the intent-to-treat population, the per-protocol population or the population of patients with bone mets at baseline. The hazard ratio does not cross 1 for the two subpopulations but the difference is not clinically meaningful.

[Slide]

This slide, based on the applicant's analysis, shows you the median time to disease progression results in the three populations. The second column from the left gives you the patient numbers on the treatment arm and the events column next to it gives you the percentage of event. These remain reasonably consistent across the three

populations. There are about 78-82 percent events on the placebo arm and 73-75 percent on the atrasentan arm. The median number of days to time to disease progression is about 85 on the placebo arm and 91 on the atrasentan arm. The difference of 4-7 days is of questionable clinical significance.

We can conclude that the difference in median time to disease progression, regardless of the population and regardless of the hazard ratios, is of little clinical relevance.

[Slide]

Next I will discuss the reliability of the difference in radiological time to disease progression in the Phase 3 study. Let's talk about a hypothetical situation first. We have a two-arm trial in which all patients on arm A have tumor progression two weeks into the study. Each and every patient on arm B has tumor progression at ten weeks. However, the time to disease progression will be 12 weeks for both arms when the imaging study is done at 12 weeks. We are unable to

identify a two-month difference in time to disease progression on the two arms in this hypothetical situation.

[Slide]

It follows that the time to radiographic progression in this case is the time to the imaging study. Any minimal difference observed is due to differences in scheduling on the two arms. We know that about 75 percent of events in the Phase 3 studies were of radiographic progression. These events drove the results of the study.

We also know that the imaging is scheduled for every 84 days. It may have been performed some days before or after this time. When we say that the median time to disease progression is 89 days on the atrasentan arm we are saying that the scans identifying the event were performed at 89 days. When the time to progression is within the same cycle for both arms we cannot reliably identify differences in time of actual event. This holds true for the per-protocol population and for the patients with bone mets at baseline. We cannot say

with any confidence that the atrasentan arm was better than placebo.

[Slide]

Most of the imaging events were observed on bone scans instead of CT scans. The slide shows you mean time to bone scan on each arm. The left column gives you the prespecified time to bone scan. The middle and right columns give the mean time of actual bone scan in weeks and standard deviations on the two arms. The standard deviation itself is about a week to two weeks. Any difference in time to disease progression less than the standard deviation may well jut be due to scheduling of imaging studies.

[Slide]

Retrospective subgroup analyses are generally considered by FDA as exploratory. With many analyses opposing results are possible. The table in this slide is taken from the applicant's study report. It shows time to disease progression in the ITT population and multiple subgroup.

Subgroups highlighted with a grey

background have a hazard ratio less than 1 and appear to support atrasentan. An example would be the subgroup with bone mets at baseline with the hazard ratio of 0.81 and p value of 0.013. On the other hand, subgroups in violet have a hazard ratio greater than 1 and appear to be harmed by atrasentan. An example would be the patients without mets at baseline, in the last line, with the hazard ratio of 9 and a p value of 0.012.

[Slide]

Let's talk about pain and compare the mitoxantrone study and the submitted atrasentan study. Pain was not identified as a primary endpoint or even secondary or tertiary endpoint for the atrasentan study. Conversely, pain was the primary endpoint for the mitoxantrone study and the basis for its approval was improvement in pain.

The mitoxantrone study used a prespecified scale to measure the intensity of pain and to monitor the duration of pain improvement. Mitoxantrone and prednisone demonstrated a two-point decrease from baseline on a six-point

scale that lasted at least six weeks in 29 percent of patients in the mitoxantrone combination arm versus 12 percent patients on the prednisone alone arm. Patients crossing over from the prednisone alone arm showed a 19 percent response. The median time to progression was improvement from 2.3 months on the prednisone alone arm to 4.4 months on the mitoxantrone combination arm. This improvement was in comparison to an active control and not a placebo as in the atrasentan study.

In contrast, the atrasentan study did not assess improvement in severity, nor did it monitor the duration of pain relief. Clearly, the magnitude of the effect was small in the atrasentan analysis and duration of effect was not considered.

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The applicant has proposed that the time to first adverse event of bone pain supports the clinical benefit of atrasentan. To be robust, the bone pain adverse event endpoint would need to be measured systematically. There was no requirement for routine assessment of bone pain in the adverse

event reporting procedures. Using data from adverse event reporting can be misleading because patients were not specifically asked to describe their bone pain at each study visit.

Let me give you an example of adverse event reporting from the study. According to the adverse event data, 12 percent of the patients on the atrasentan arm were reported to have prostate cancer as an AE versus 16 percent in the placebo arm. As all the patients in the trial were required to have documented prostate cancer, using the AE data would suggest that atrasentan and placebo cured over 80 percent of patients with prostate cancer.

[Slide]

It would be worthwhile to go over the time line for the atrasentan Phase 3 study and the bases of efficacy analyses. In March, 2003 the study was closed early based on the recommendation of the data safety monitoring board because it failed to demonstrate efficacy. In December, 2004 an NDA with a large number of efficacy analyses, all

serving as a basis of efficacy, was submitted. In April, 2005 the FDA requested that some statistical adjustments should be made for the multiple analyses and that a primary basis of efficacy should be identified.

In June, 2005 the applicant identified time to disease progression in the population with bone mets at baseline as the basis of efficacy. Seven months into the review process, in July, 2005 the proposed indication was changed to this retrospectively identified subgroup. In August, 2005 further new analyses were submitted in the briefing document. For the first time Abbott made the distinction of clinical versus radiological disease progression in their analyses.

Radiologic progressions were said to be of little direct clinical significance, however, radiologic progressions, if unchecked, will result in morbidity. It is the magnitude of the results that puts the clinical relevance of radiographic progressions in doubt.

Analysis of 50 percent improvement in pain

was another new analysis submitted in the briefing document. Because no events after the first one were captured in the CRF censoring at three months it would result in loss of a large amount of data and we have additional weaknesses of a retrospective analysis.

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So far we have shown that only the Phase 3 efficacy data are evaluable. The design definition and population of the Phase 2 study was different from the Phase 3 study. The results from the Phase 2 study cannot be pooled with the Phase 3 study and cannot be used to support the results of the Phase 3 study. Primary and secondary endpoints failed. Where a secondary endpoint reached unadjusted statistical significance it was of questionable relevance. Bone marker and quality of life endpoints in the secondary and tertiary prespecified analyses failed. The difference of only a few days in time to disease progression is of questionable clinical relevance and reliability whether it is the intent-to-treat population,

per-protocol population or the population of patients with bone mets at baseline. Multiple post hoc analyses warrant further studies.

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The formulation used in the Phase 3 study was different from the Phase 2 study. They were not bioequivalent by FDA standards. AUC was the same but the Cmax differed in the two studies. The safety results will, therefore, not be combined. Rather, the first major safety concerns from the Phase 3 study will be presented, followed by safety results from the Phase 2 studies for corroboration. I will present only some of the more serious adverse events observed on these studies. Death occurring on treatment or within 30 days of last treatment will be reported.

[Slide]

Although survival was similar, numerically there were more deaths on the atrasentan arm. There were 41 percent deaths on the atrasentan arm when compared to 39 percent on the placebo arm. Deaths from cardiovascular causes were also greater

on the atrasentan arm. Grade 3 or 4 coronary artery disorders, CHF and pneumonia were greater on the atrasentan arm in the Phase 3 study.

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Myocardial infarctions, angina pectoris and coronary artery disorders were the COSTART terms included in the category of coronary artery disease. One of the coronary artery disorder patients required stent placement. The second patient had some diagnosis therapeutic procedure performed that was not further specified.

As you can see, eight patients in the atrasentan had grade 3 or 4 coronary artery disorder events on the Phase 3 study versus only two on the placebo arm. There were two deaths on the atrasentan arm and one death on the placebo arm.

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An increase in coronary artery disease was also noted in the Phase 2 study whether it is angina pectoris, coronary artery disease or myocardial infarctions. Seven percent of patients

on the atrasentan 10 mg arm had a coronary artery disorder event versus less than 1 percent on placebo. One patient on the atrasentan 10 mg arm died from a heart attack and one on the 2. 5 mg arm.

[Slide]

There was an increase in arrhythmias on the atrasentan arm of the Phase 3 studies. Twenty patients on the atrasentan arm suffered from arrhythmias compared with five patients on the placebo arm. If one removes the cases with palpitation from the analysis, there were 17 patients on the atrasentan arm who had arrhythmias versus four on the placebo arm.

As in the Phase 3 study, more patients on the atrasentan arm had arrhythmias when compared to placebo. Seventeen patients on the atrasentan arm suffered from heart failure versus three patients on placebo. Eleven patients on the atrasentan arm had grade 3 or 4 CHF and there were six deaths on this arm from CHF. One patient on the placebo arm had a CHF-related death.

[Slide]

Increased incidence of heart failure on both atrasentan arms was observed in the Phase 2 study as well.

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In conclusion, the statistical plan specified that if the primary endpoint fails the study will have failed. Not only did the primary endpoint fail, the secondary endpoints failed, or their magnitude was not clinically meaningful. Many tertiary endpoints failed. These prespecified failed endpoints included bone markers and some quality of life analyses.

Retrospective analyses tend to have a high false-positive rate. These data do not convincingly prove the efficacy of atrasentan. The pain endpoint was analyzed post hoc and the magnitude of change in the unvalidated pain scales was small. Additionally, there are safety concerns regarding coronary artery disease, arrhythmias and CHF on the Phase 3 study, corroborated by an increased incidence of these toxicities on the

Phase 2 study. Finally, atrasentan was compared to placebo and not an active control.

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We have seen that the study results are not robust. The DSMB recommended early closure of the studies based on lack of efficacy. The prespecified primary endpoint failed. We have also seen that the results were not persuasive statistically or clinically, and some signals for serious cardiac toxicity have been observed.

Additionally, FDA has results of a study in an earlier stage of prostate cancer which have not been reviewed or published at this time. This study also failed. Other studies of atrasentan in men with prostate cancer are being planned. We come to this question, based on the results reviewed, does this drug warrant further study before consideration of widespread use? Thank you.

DR. MARTINO: Thank you. Dr. D'Agostino, you have a few moments, please.

Subgroup Analysis

[Slide]

DR. D'AGOSTINO: What I have been asked to do is just to talk a little bit about the use of subgroups in clinical trials. I am going to talk fast and I am going to talk about clinical scenarios, subset analyses and I am going to try to illustrate good and problematic practice. I am going to look at interaction tests in this context. I am going to talk about some statistical properties and then I am going to close.

[Slide]

There are I think many, but two in particular, ways of approaching the subset analysis. One is that you have, as these studies seem to be, all your data combined and you are going to perform a statistical test. If that test produces significance--treatment one is different than treatment two--then you start looking at subsets for consistency. You may along the way even have special subsets that you are interested in looking at. Both of these activities, looking at subsets and looking at special subsets, are secondary analyses. The primary analysis is the

overall.

In contrast to that, you may have at the beginning, before you start looking at your data, some subgroups which you think are going to be different or you think are going to be of interest and you start right off looking at those subsets and you try to justify pooling or you analyze them separately. So, two scenarios.

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The first one is the one that I believe was done with the data we have before us where there were two treatments under consideration and there was an overall analysis performed. The overall analysis is looking at the difference between the two treatments without a subset. Now, if we go to that type of scenario--forget the data before us, if we go to that type of scenario we look at all the data and we test treatment one versus treatment two and, say, it turns out to be statistically significant we move on to say, well, we want to make sure that there is consistency in our data. So, we start looking at subsets. These

subset analyses are all secondary.

[Slide]

The overall test is significant. You get this type a lot, treatment one. This would be time to occurrence of event. Treatment one looks better than treatment two, statistically significant difference.

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Then you look at subsets. Now, when you look at subsets you haven't powered your tests for the subsets. You do the overall test and if it is significant then you start seeing, well, are there difference males, females, ages, some previous condition, and so forth and so on. Many of these subsets aren't going to be significant because you didn't power but you are looking for consistency--treatment one looks better than treatment two, overall significance, and these subset analyses may be a hazard ratio with confidence intervals.

[Slide]

You might have a special subset, say,

location of brain cancer versus no. Some of your subset analyses will focus on that again as a secondary analysis. You might get a nice paper saying this is a secondary analysis but it is a secondary analysis. Overall is the significance and then consistency with the subsets.

[Slide]

Here is an example from the cardiovascular looking at Clopidogrel versus aspirin and looking at the reduction of some ischemic events. The overall was significant. Clopidogrel looked statistically better than aspirin.

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We looked at the initial events, how people got in the study--ischemic, strokes, the zero line with Clopidogrel better on this side, aspirin better on this side. The overall result said that Clopidogrel was better. Then we looked at some subsets, ischemic strokes as entry, myocardial infarctions and peripheral arterial disease. There was really thought that maybe peripheral arterial disease was going to look

better and it certainly did. This is the type of idea, overall analysis consistency with subsets.

[Slide]

Now, if the overall test isn't statistically significant basically, and you have heard it over and over again but I am going to repeat it, technically you can't do anything with statistical statements beyond this point. You can look at subsets but it is really exploratory. You don't even want to call them secondary.

[Slide]

The original data looks something like this, no significance, but you say let me look at subsets and you get things like this happening. The overall isn't significant. You don't see anything in males and females but you look down and you say, my God, age over 65 and you start generating a theory on why age over 65 should be significant. All of this is just basically exploratory and leads to something further but is inappropriate for labeling with statistical significance.