DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

70TH MEETING

Thursday, January 31, 2002

8:00 a.m.

Advisors and Consultants Staff Conference Room
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

Stacy Nerenstone, M.D., Chairperson
Karen M. Templeton-Somers, Ph.D., Executive Secretary

MEMBERS

Kathy Albain, M.D. (By Videoconference)
Otis W. Brawley, M.D.
Stephen L. George, Ph.D.
David P. Kelsen, M.D. (By Teleconference)
Scott Lippman, M.D.
Jody L. Pelusi, F.N.P., Ph.D.
(Consumer Representative)
Donna Przepiorka, M.D., Ph.D.
Sara A. Taylor, M.D. (By Videoconference)

VOTING CONSULTANT

Derek Raghavan, M.D., Ph.D.

NON-VOTING GUEST SPEAKERS

Philip Bonomi, M.D.
Patrick J. Loehrer, M.D.

VOTING PATIENT REPRESENTATIVE

Eugene J. Kazmierczak

FDA

Amna Ibrahim, M.D.
Richard Pazdur, M.D.
Nancy Scher, M.D.
Robert B. Temple, M.D.
Grant Williams, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. NERENSTONE: I would like to welcome everyone to ODAC, our 70th meeting. We still start with our usual introduction of the committee. Kathy, can you hear us?

DR. ALBAIN: Yes; I can. Good morning.

DR. NERENSTONE: Why don't you start with the introductions. We will go around the table. You are first.

DR. ALBAIN: Kathy Albain, medical oncology, Loyola University, Chicago.

DR. LOEHRER: I am Pat Loehrer from Indiana University.

DR. BONOMI: Phil Bonomi, medical oncology, Rush University in Chicago.

DR. RAGHAVAN: Derek Raghavan, U.S.C. in Los Angeles.

DR. GEORGE: Stephen George, Duke University.

DR. LIPPMAN: Scott Lippman, M.D. Anderson Cancer Center.

MR. KAZMIERCZAK: Gene Kazmierczak, patient representative.

DR. PRZEPIORKA: Donna Przepiorka, Baylor

at Houston.

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

DR. NERENSTONE: Stacy Nerenstone, medical oncology, Hartford, Connecticut.

DR. BRAWLEY: Otis Brawley, medical oncology, Emory University, Atlanta.

DR. PELUSI: Jody Pelusi, oncology nurse practitioner, Phoenix Indian Medical Center and consumer rep.

DR. SCHER: Nancy Scher, medical oncology, FDA.

DR. IBRAHIM: Amna Ibrahim, medical officer, FDA.

DR. WILLIAMS: Grant Williams, medical team leader, FDA.

DR. PAZDUR: Richard Pazdur, Division Director, Oncology Drugs, FDA.

MS. TEMPLETON-SOMERS: I would like to welcome everyone to our conference room here in our office. It is unusual for us to hold ODAC here but this is sort of an unusual ODAC, a meeting with a late addition to our schedule and so our hotel choice was very limited. We apologize in advance for any crowding, for the crowd, mostly, but we

thought it was important to get the meeting scheduled in January rather than waiting for our regularly scheduled meeting in late February.

This meeting is also ground-breaking in that it represents our first steps into the world of having member participation by electronic means. Dr. Kathy Albain and, hopefully, Dr. Sarah Taylor are participating by videoconferencing from their home bases in the Midwest. Sarah may not be joining us because we have heard news that Kansas City has no power due to the snow storm. So even electronic means are not going to get around that. Kathy was saying that she might be grounded in the airport, too.

Dr. Kelsen will be joining us from New York by a combination of webcasting, by which he is going to watch the proceedings, and teleconferencing.

I am going to go right into the conflict of interest.

Conflict of Interest Statement

MS. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of record to preclude even the appearance of

such at this meeting.

Based on the submitted agenda an information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 USC 208(b)(1), Jody Pelusi, R.N., Ph.D., has been granted a waiver for serving on an advisory board for a competitor and for her speaking for a competitor. She receives less than $10,000 a year for her participation on the advisory board and from $5,000 to $10,000 a year for her speaking.

In addition, Scott Lippman, M.D., has been granted a waiver under 18 USC 208(b)(3) for his consulting for a competitor on unrelated matters. He receives from $10,000 to $50,000 a year for his consulting.

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

With respect to FDA's invited guests, Dr.

Philip Bonomi has a reported interest that we believe should be made public to allow the participants to objectively evaluate his comments. Dr. Bonomi is a scientific advisor for Genentech and OSI.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have 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 product they may wish to comment upon.

Thank you.

DR. NERENSTONE: We will go now to the open public hearing part and Ann E. Fonfa from the Annie Appleseed Project. The letter will be read.

Open Public Hearing

MS. TEMPLETON-SOMERS: This letter is a statement from Ann Fonfa of the Annie Appleseed Project. "I am Ann Fonfa, a breast-cancer survivor and activist, founder of the Annie Appleseed

Project which educates, informs, advocates and raises awareness for those cancer patients, family and friends interested in or using complementary alternative natural therapies.

I have just finished giving NCI input on their consumer guide for clinical trials in that they show that most drugs take about fourteen years to reach the approval stage. My question to this body is why are we spending thousands of human subject hours in constantly approving drugs that are little better than the ones we cancer patients already have access to.

There is something wrong with this entire system when the best that we can do is offer a drug that has just about the same safety profile, just about the same response results but differs in a very minor way. We patients are, therefore, condemned to live out our lives, however long that may be, with no real advances in treatments.

I resent this and I am taking this opportunity to say so. Aim higher. We are all tired of crawling on our hands and knees through a field of broken glass. We want to leap over it and, for that, we need new drugs that are different and that make a real difference in our lives.

Thank you for your attention. If you would like to find out more about our organization, please go to our website, www.annieappleseedproject.org.

FYI, I completely support the idea of bisphosphonates for treatment of metastatic bone disease."

DR. NERENSTONE: Are there any other people for the open public hearing?

Seeing no one, then we will turn now to the supplemental NDA for Zometa indicated for the treatment of bone metastases in patients with multiple myeloma, breast cancer, prostate cancer and other solid tumors. Novartis will start with their sponsor presentation.

NDA 21-386, Zometa (zoledronic acid for injection)

Novartis Pharmaceuticals Corporation

Introduction

DR. DALDRUP: Dr. Nerenstone, Dr. Pazdur, Dr. Williams, members of the advisory committee, FDA and guests, good morning.

[Slide.]

My name is Burkhard Daldrup. I am Global Head of Drug Regulatory Affairs for Novartis Oncology. On behalf of Novartis, I would like to

thank you for the opportunity this morning to present and review our Zometa data for a new indication in the treatment of bone metastases.

[Slide.]

Zometa belongs to a new class of highly potent bisphosphonates. In August 2001, Zometa was approved by FDA for its first indication of therapy for the treatment of hypercalcemia of malignancy. Zometa is currently approved for this indication in more than sixty countries around the world.

A dossier for the treatment of bone metastases was filed in July 2001 in Europe and a supplemental application was also submitted in August 2001 in the U.S. as well as in many other countries.

The recommended dose is 4 milligrams infused over 15 minutes administered every three to four weeks. Novartis is also evaluating nononcologic indications for Zometa including, at this time, Paget's disease, osteoporosis and rheumatoid arthritis.

[Slide.]

Specifically, we are seeking FDA approval for the following proposed indication. Zometa is indicated for the treatment of osteolytic,

osteoblastic and mixed bone metastases of solid tumors and osteolytic lesions of multiple myeloma in conjunction with standard antineoplastic therapy.

[Slide.]

Three phase III trials form the basis of this supplemental NDA. These trials are the largest randomized studies ever conducted in the treatment of bone metastases. Study 010 is a pivotal, randomized, double-blind, double-dummy study comparing Zometa to pamidronate in patients with multiple myeloma and breast cancer. In this study, patients were treated for thirteen months.

Studies 039 and 011 are pivotal, randomized, double-blind, placebo-controlled trials. Study 039 was conducted in patients with prostate cancer over fifteen months. Study 011 was conducted in patients with non-small-cell lung cancer and other solid tumors over nine months.

The clinical program was discussed with the FDA and other major health authorities from around the world.

[Slide.]

The data derived from these three large pivotal studies support the following clinical

profile for Zometa. Zometa, given at a dose of 4 milligrams every three to four weeks is bone specific not tumor specific as Zometa shows effectiveness in a broad variety of different tumor types studied.

The clinical trials involved patients with breast cancer and multiple myeloma as well as patients with prostate cancer and other solid tumors. Other bisphosphonates have not demonstrated efficacy in these latter tumor types to date.

[Slide.]

So Zometa is the first bisphosphonate shown to be effective for the treatment of bone metastases over a wide variety of tumor types. Cumulative safety experience from all trials in the treatment of bone metastases indicates that the safety of Zometa at a dose of 4 milligrams infused over 15 minutes is comparable with that of i.v. pamidronate 90 milligrams, the current standard of care for patients with multiple myeloma and breast cancer.

The overall safety profile of Zometa is supported by data from more than 3,000 patients treated to date.

[Slide.]

This morning, we would like to present to you detailed data on the safety and efficacy of Zometa in the treatment of bone metastases. First, Dr. Robert Coleman will give an overview of the pathophysiology of metastatic bone disease and the role of bisphosphonates. Dr. Coleman is Professor of Medical Oncology at the Cancer Research Center at Weston Park Hospital in Sheffield, U.K.

Dr. James Berenson will then present the data on Zometa in the treatment of breast cancer and multiple myeloma, study 010. Dr. Berenson is Director of the Multiple Myeloma and Bone Metastases Programs at Cedar Sinai Medical Center in Los Angeles.

Dr. Paul Gallo, Assistant Director of Biostatistics, Novartis, will provide also some clarification on the statistical analysis for study 010.

Then, after FDA's presentation and discussion by the committee, Dr. Matthew Smith will continue with a discussion of the role of Zometa in prostate cancer. Dr. Smith is Professor of Medicine at Massachusetts General Hospital, Boston, and was an investigator for study 039.

Dr. Coleman will then return to discuss the role of Zometa in the treatment of solid tumors other than breast and prostate cancer, study 011.

Finally, Dr. David Parkinson will present the overall summary and conclusions. Dr. Parkinson is Vice President and Global Head for Clinical Research at Novartis Oncology.

[Slide.]

In addition to the presenters for today, we also have several clinical experts and advisors with us who are available to help answer specific questions the committee may have. Dr. John Seaman will field responses to the committee's questions and provide background regarding the Zometa Clinical Research and Development Program. Dr. Seaman in the International Team Leader for Zometa at Novartis Oncology.

For biostatistical aspects, we have two consultants in attendance, Dr. Richard Cook who is an Associate Professor at the University of Waterloo in Ontario, and Dr. Thomas Fleming, who is Professor and Chair of the Department of Biostatistics at the University of Washington in Seattle.

Clinical experts with us today are Dr.

Pierre Major, medical oncologist at the Hamilton Regional Cancer Center in Ontario and Associate Professor at McMaster University; Dr. Joseph Simeone, Professor of Radiology at Harvard Medical School; and, representing the Renal Advisory Board which has closely monitored the renal safety of Zometa during development, Dr. Raimund Hirschberg, nephrologist and Professor of Medicine at the Harbor UCLA Medical Center in Torrence, California.

I would now like to turn the podium over to Dr. Robert Coleman for an overview of the pathophysiology of metastatic bone disease and the role of bisphosphonates.

Dr. Coleman, please.

Pathophysiology of Metastatic Bone Diseases and the Role of Bisphosphonates

DR. COLEMAN: Good morning.

[Slide.]

Dr. Nerenstone, members of the ODAC panel, ladies and gentlemen. This morning, to provide the background information to today's presentations, there are really four aspects that I would like to get across to the panel over the next twenty to twenty-five minutes.

These are the clinical importance and

consequences of metastatic bone disease. The second is the underlying pathophysiology and some of the similarities that exist across the range of tumor types that affect patients; thirdly, the experience with previous bisphosphonates, notably pamidronate, in the management of metastatic bone disease; fourthly, the background information of zoledronic acid in terms of its pharmacology and the rationale for its dose and schedule in the trials you are going to hear about.

[Slide.]

Turning first to the clinical importance and prognosis of bone metastases, this slide shows a number of tumors that commonly spread to bone. They are listed in the order that you might associate with the radiographic spectrum of disease that we see on plane X-rays. In other words, at the top is myeloma, typically a very lytic condition. At the bottom is prostate cancer which we associate more with a blastic condition. In between are tumors that have a varied appearance of lytic mixed and blastic.

This slide also shows the disease prevalence in the United States and makes the point that, particular for breast cancer and prostate

cancer, we have an enormous clinical burden to deal with.

That is made doubly important when you look at the incidence of bone metastases that typically complicates advanced disease with, perhaps, three-quarters or even four-fifths of patients with breast cancer and prostate cancer developing bone metastases during the course of their illness.

The right-hand part of the slide shows the median survival after development of bone metastases and makes the point that, for many of these conditions, particular breast and prostate cancer, the median survival is measurable more in years than in months. So this is a chronic condition requiring long-term palliative therapy.

[Slide.]

The disease causes a number of very important complications, very important to the patient and very important to our healthcare resources. The complications that we see from bone metastases are shown in this slide and include radiation therapy to bone, pathological fractures, either of long bones or vertebral bodies, hypercalcemia and malignancy, surgery to bone and,

in some cases, spinal-cord compression.

This slide is designed to try and give you a feel for the proportion of patients that experience these events on standard therapy. They are taken from the placebo arms of randomized trials that were assessing bisphosphonate use. But these figures related to the placebo arms of either pamidronate or Zometa trials.

I think they show that, across the board of disease, breast, prostate and other tumors, that these complications are common, perhaps three or four occurring per year in a typical patient. About one-third of patients with breast cancer have relatively similar proportions with other diseases and will require radiotherapy and a similar number would experience a pathological fracture.

Obviously, some of the other events are less common but sometimes more clinically significant.

[Slide.]

Having outlined that clinical importance, I want to move on to the pathophysiology. This first slide is a very simplistic view of the relationship between tumor cells and bone cells. But it serves to make the point that osteoclast

activation--in other words, the acceleration of bone resorption--is very important in the crosstalk between tumor cells and bone.

Tumor cells, as most of us will know, reach the target organ through the circulation and are attracted to bone surface by a variety of cytokines and growth factors which are probably released from bone.

If the tumor cell possesses the right machinery to produce relevant cytokines and growth factors, it is able to stimulate osteoclast activity, either directly or through bystander cells, to resorb bone. That resorption of bone, as you will see, is responsible for most of the complications.

There is also a feedback loop where bone cytokines and bone growth factors may stimulate the proliferation and growth of tumor cells in the biomicro environment.

The third mechanism that is illustrated on that slide is is there a direct effect of cancer cells on bone which is, perhaps, independent of the osteoclast. That is an area under research but, to date, it has been extremely difficult to demonstrate any direct destruction of bone by tumor

cells in either the clinic or in animal-tumor models.

So, to the best of our knowledge, by far, the major pathway is through osteoclast activation.

[Slide.]

How does this pathway differ between what you see on x-rays in osteolytic disease and what you appreciate as an osteoblastic osteosclerotic lesion, typical, perhaps, of prostate cancer of some breast patients.

This slide shows that same loop of osteoclast activity, both for lytic and for blastic disease. The osteoclast loop is very similar for both ends of the spectrum. Of course, osteoclast disease is associated with excessive new bone formation and there are growth factors and cytokines produced by prostate cells and other blastic-inducing tumors that stimulate bone formation.

But that bone formation is probably not of huge clinical importance. It is not contributing greatly to the structure of the underlying bone. So, across the spectrum, that osteoclast process appears to be very important.

[Slide.]

That disturbance of bone-cell function leads to changes in bone remodeling. Bone remodeling is essential. it is going on in all of us. It is essential to maintain the structural integrity of bone. It is necessary to replace old and fatiguing bone with replacement by new and healthy bone. Usually, that process is coupled and balanced; in other words, areas of bone resorption are repaired in the right quantity and in the right place by the various coupling signals that exist in the bone microenvironment.

Cancer disturbs that process in a number of ways. This diagram shows what we associate with osteoclast disease. There are excessive numbers of resorption cavities and the skeleton is unable to repair that damage at a rate that maintains structure integrity in either trabecular or cortical bone. So, gradually, the bone thins and fractures.

In mixed lesions, this is the appearance that appears to be happening from histomorphometric studies in that, yes, there is new bone formation but it is in the wrong place and there is still unopposed bone resorption. This process is even more marked in osteosclerotic disease where there

are excessive amounts of new bone formation. But, again, in the majority of resorption cavities, it is not applied in the right place. It is laid down on creascent bone surfaces and is not really contributing to bone strength.

[Slide.]

How do we know that? There have been a number of publications, which I don't have time to go into, of histomorphometric studies of bone metastases showing the importance of osteoclast activity across the range of conditions. This slide shows one of many studies that have looked at bone markers, or bone formation and bone resorption, and shows the effect of either lytic or mixed or sclerotic disease on a well-known marker of bone formation, alkaline phosphatase or on a marker of bone resorption, the N-telopeptide, which is a collagen fraction, in this case measured in urine.

On the left is the bone formation. Of course, as you would expect, bone formation is massively increased in osteoblastic disease and normal, or even subnormal, in lytic and mixed disease.

What is of interest in this slide is that,

when we look at bone resorption, bone resorption rates are massively increased in osteoblastic disease. Of course, they are increased in lytic disease as well but, if anything, they are even more greatly increased in the osteoblastic patients. So I think that gives you some biochemical evidence for the importance of bone resorption across the range of conditions that might affect bone.

[Slide.]

As I have hinted, by and large, increased bone resorption is what is responsible for the problems that the patient complains of in the clinic, some aspects of the pain, certainly the fractures and the hypercalcemia that patients may different.

[Slide.]

So, turning now to treatment. Of course, we all recognize there are many treatments out there for the management of these patients. Most of these treatments are going to remain important for the foreseeable future. Bisphosphonates, I think by all of us, are seen as a complementary approach. In other words, they are usually used in addition to standard therapy, either endocrine or

chemotherapy as appropriate.

But, as you will see, they may reduce the requirements for some other modalities, such as radiation to bone, surgical intervention and, perhaps, some aspects of analgesic use.

[Slide.]

The bisphosphonates are quite a large class of agents and they have relatively similar pharmacology in terms of their effects on bone cells. This cartoon summarizes the three principal mechanisms that we are aware of. Firstly, all bisphosphonates bind very avidly to calcium, so they bind to the bone surface and the hydroxyapatite and they make it very difficult for the osteoclast to adhere to that bone and resorb it.

Secondly, they have direct effects on osteoclast function and activity through biochemical pathways and the indication of apoptosis. Thirdly, at least myobisphosphonates have the ability to affect production and maturation of osteoclasts.

[Slide.]

So what is the use of bisphosphonates at the moment in the conditions that we are discussing

today. There is a lot of uncontrolled data but I am going to concentrate on the phase III pamidronate studies in breast cancer, myeloma and prostate cancer that are available to us.

These have looked at various endpoints but predominantly at prevention of skeletal-related events. Firstly, looking at breast cancer and myeloma, there are five important studies of note, four in breast cancer and one in myeloma.

In terms of the breast-cancer patients, they really fall into two groups. The first were two studies performed in Europe with doses of 45 or 60 milligrams of pamidronate--in other words, below the current recommended dosage, which used, as an endpoint, time to progression in bone assessed by radiologists not involved in the study.

These studies did show an improvement of time to progression in bone of three to four months but did not show significant effects on skeletal-related events at the doses used. They were then followed by the better-known international trials published by Theriault and colleagues and Hortobagyi and colleagues which led to the registration of pamidronate in this country and worldwide.

These trials recruited breast-cancer patients with at least one predominantly lytic lesion plus or minus mixed or blastic lesions as typically occurs in our patient population and included either patients on endocrine therapy or patients on chemotherapy at study entry and I think showed quite clearly that pamidronate was able to reduce the frequency of skeletal events, the number of events per unit time and also the time to skeletal events by about 10 to 13 percent.

In multiple myeloma, the study from Berenson et al., showed similar results and led to the use of pamidronate worldwide in multiple myeloma again showing a significant reduction in the proportion of skeletal-related events. So I think there is little doubt that pamidronate works in these two conditions.

[Slide.]

Let's just look at those data in a little more detail, first the two pivotal breast-cancer studies which have been amalgamated here as part of publication from Anna Lipton and colleagues. It is showing the results both at twelve months, which is close to the analysis you will hear for Zometa later, and at 24 months, a later follow-up

analysis.

It shows an 11 percent reduction in the proportion of patients experiencing a skeletal event at twelve months which increases slightly more at 24 months. It is very clear from this slide that the effect is quite marked in terms of effects on radiation to bone and pathological fractures and is maintained, or even increases, as time goes by.

[Slide.]

This slides shows a similar analysis but for multiple myeloma, again, a short-term analysis at nine months and a follow up analysis at 21 months, again showing an improvement in absolute terms of around 17 percent at nine months in terms of the proportion of patients with skeletal events.

This effect is maintained out to two years and includes both effects on radiation requirements and fractures.

[Slide.]

As a clinician, I sometimes find it difficult to assimilate proportions of patients experiencing events and so I include this slide which gives a flavor of the totality of events that occurred in these studies and shows that about 40

percent of events were abolished by the addition of pamidronate to underlying systemic therapy whether you look at either the breast-cancer protocols or the multiple-myeloma protocol.

You can see that it affected important events like requiring surgery, requiring radiotherapy and nonvertebral long-bone fractures.

[Slide.]

In addition, pamidronate and intravenous bisphosphonates in general can have beneficial effects on pain and analgesic consumption. This slide shows this pain and analgesic results from the three pivotal pamidronate trials. Of course, as patients live with their cancer over a period of two years or so, by and large, they deteriorate. Their performance status deteriorates. They require more analgesics and they have more pain.

But what this study shows was that the addition of pamidronate slowed that deterioration and reduced in increase that most patients would experience in analgesic requirements. For multiple myeloma, at least at the nine-month analysis, there was actually a reduction in analgesia requirements and pain compared to the placebo-treated patients.

[Slide.]

What about other tumors? Well, here we have far fewer data with pamidronate and, indeed, any other bisphosphonate prior to Zometa. As I have indicated, there is biochemical and histomorphometric evidence of increased bone resorption with osteosclerotic metastases and there are reports in the literature, somewhat anecdotal, perhaps, but, nevertheless, of useful pain relief from acute high-dose bisphosphonate treatment for sclerotic metastases or other tumors.

But no previous randomized trial evidence exists to date that shows a beneficial effect of bisphosphonates on skeletal events.

[Slide.]

The only study that is really available to present to you today is a trial that was conducted with pamidronate and which has been presented in abstract form which was a relatively short-term study of only six months duration with a primary endpoint, actually, of pain rather than skeletal events. But, as far as this study can show, pamidronate was unable to influence the pattern of skeletal events, the number of patients who experienced a skeletal event or the skeletal morbidity rate.

So we don't have any evidence in prostate cancer to date that pamidronate or any other bisphosphonate is particularly useful apart from, perhaps, treating pain.

[Slide.]

What about adverse-event profile of bisphosphonates? In general, these are very well-tolerated compounds compared to many of the things that we use in oncology. Intravenous bisphosphonates are associated with the acute-phase response classically comprised of fever, myalgia, arthralgia. There is an increased incidence of anemia for uncertain reasons with bisphosphonates and occasional mineral disorders such as hypercalcemia and hyperphosphatemia.

Very importantly, there are renal effects of bisphosphonates which are seen as a class effect and are very much related to the dose given and particularly the infusion time over which the dose is administered. That is seen with cadrinate*, pamidronate and almost any other intravenous bisphosphonate.

[Slide.]

How does zoledronic acid differ? Well, it is more potent, at least in the laboratory

situation, and it is more potent because of this unique structure where, on the site of the PCP backbone, or bone hook, is this imidazole side chain with these two nitrogen atoms which increases its potency above any other bisphosphonate currently in development.

[Slide.]

There are a number of key preclinical properties of Zometa. First, in vitro, it has been shown to potently inhibit osteoclast formation and bone resorption really regardless of the underlying pathogenic stimulus and, in vivo, is able to inhibit bone resorption in a variety of benign and malignant bone-disease models, again irrespective of tumor types.

It does this without deleterious effect on bone structure in that it preserves bone architecture and strength and does not inhibit bone formation.

Interestingly and, perhaps, not of direct relevance today, but Zometa also has novel effects of angiogenesis and on pain and neurotransmitter production. Lastly, in a number of animal models where tumor cells have been inoculated into animals, it has been shown that treatment with

bisphosphonates such as Zometa is able to reduce the number and size of bone metastases and inhibit much of the tumor-induced osteolysis associated with those animal models.

[Slide.]

In terms of the pharmacology, Zometa is very similar to other bisphosphonates. There is very little protein binding or uptake by red blood cells and no significant interaction with cytochrome P450 metabolizing enzymes.

In vivo, there are similar pharmacokinetics in that, after intravenous administration, there is a rapid disappearance of the drug from circulation and the plasma drug concentrations are dose-proportional. Most of an infused dose goes to bone, perhaps about 60 percent, and the rest is rapidly eliminated by the kidney over approximately 24 hours.

[Slide.]

There have been studies of Zometa in patients with renal dysfunction. This slide summarizes the area under the concentration curve for 24 hours of Zometa given on three occasions to three different groups of patients, either with normal renal function, mild impairment or moderate

renal dysfunction.

It shows that, at least down to a creatinine clearance of 30, that although this is associated with a small increase in AUC, it has no effect on urine excretion and the increase in AUC is not affected by repeated dosages. There is no accumulation of the compound with time.

On the basis of these studies, there is no indication as, indeed, there is no indication for pamidronate, to dose reduce in renal impairment at least down to clearance of 30 mls per minute.

[Slide.]

What about the dose and schedule for use in oncology patients? Well, a lot of data has been generated on phase I and phase II trials. This slide summarizes findings from a phase II trial of some 270 or more patients, protocol 007, where Zometa was given in addition to standard therapy to a population of breast cancer and myeloma patients and doses of 4, 2 and 0.4 milligrams were compared to pamidronate.

This study showed that, on a three- to four-weekly schedule, that Zometa, at 2 and 4 milligrams, was able to produce sustained effects on serum and urinary markers of bone resorption but

the 4 milligram dose was the most effective dose tested. Skeletal events and pathological fractures were reduced most by the 4 milligram dose of Zometa and the 0.4 milligram dose was clearly ineffective compared to the other Zometa doses or, indeed, pamidronate.

Lastly, the time to first skeletal event in the breast-cancer patients was almost two months longer in the 4 milligram arm versus the 2 milligram dose although, being a phase II study, of course it was not powered to show this as a significant difference.

[Slide.]

Exploring the schedule and dose in a little more detail using bone markers, this slide illustrates a couple of key points. Firstly, this is taken from protocol 007. It shows the biochemical profiles of the three Zometa dosages, 0.4, 2 and 4 milligrams, and pamidronate 90 and shows that there is a rapid inhibition of bone resorption which reaches a maximum at around a week after infusion.

But the red line, the 4 milligram Zometa group, shows a more sustained effect with persisting complete inhibition of bone resorption

at four weeks whereas pamidronate and the other dosages are beginning to wear off by that time point.

The right-hand side of the slide shows the effects of chronic dosing where that effect of inhibiting bone resorption is maintained and, again, is more marked at the 4 milligram dosage than it is at other dosages tested in that study or, again, more marked than pamidronate.

[Slide.]

You have already heard in the introductory talk that Zometa is already licensed for the treatment of hypercalcemia of malignancy. This slide just reminds us of the data that led to that approval. This was a study in patients with moderate to severe hypercalcemia of malignancy and compared pamidronate 90 milligrams with Zometa at 4 or 8 milligrams and showed quite clearly that Zometa was superior with nearly 90 percent of patients achieving normocalcemia by ten days which was the primary endpoint of the study, compared to 70 percent with pamidronate.

In addition, Zometa worked more quickly and, of interest, there was no difference between the 4 and 8 milligram dosages in this trial.

Clearly, these data were not available when the phase III studies were generated and the protocols designed. But it suggests that Zometa is superior to pamidronate but there is no dose response between 4 and 8 milligrams.

[Slide.]

So, to conclude my presentation, I think we can all agree that metastatic bone disease is an important healthcare problem in oncology and there are many unmet needs for our patients in terms of skeletal complications. Although the underlying tumor biology is very different at the primary site, when the disease gets to bone, the pathophysiology is very similar in that it is mediated through osteoclasts and, as far as we can tell, osteoclast activation accompanies all bone metastases with or without bone formation.

The currently available bisphosphonates have a limited range of activity which I think we have to say is, at the present, confined to breast cancer and myeloma. Zometa is a more potent inhibitor of osteoclast activity which, we believe, provides a bone-specific treatment which is applicable across a range of tumor types.

I thank you for your attention and would

now like to turn the podium over to Dr. Jim Berenson who is going to present the first of the three phase III trials, protocol 010.

Pathophysiology of Metastatic Bone Diseases and the Role of Bisphosphonates

DR. BERENSON: Good morning all. Good morning Dr. Nerenstone, members of the ODAC, those of you who are on teleconference and videoconference this morning.

[Slide.]

It is my pleasure to present to you the first of three randomized double-blind studies evaluating Zometa at two doses. This first study involves patients with breast cancer metastatic to bone and multiple myeloma with at least one lytic lesion. Unlike the other studies, in this study, the comparator is pamidronate since, as you heard from Dr. Coleman, this has shown to be effective in reducing skeletal complications in these types of patients.

[Slide.]

This was a double-blind, double-dummy, study involving 1648 patients who were stratified prior to assignment to which drug based on *Duriei-Salmon stage III patients with at least one lytic

lesion with myeloma and then breast-cancer patients either on hormonal therapy or chemotherapy. This patients had to have stage IV breast with at least one either lytic, blastic or mixed lesion.

They could be on appropriate antineoplastic therapy at baseline and this could be changed at the discretion of the treating physician during the trial. ECOG performance status could be 0, 1 or 2 and the serum creatinine at the time of study entry had to be less than or equal to 3 milligrams per deciliter.

[Slide.]

The study design is shown here. This was a 12-month dosing study. Pamidronate was given as 90 milligrams every three to four weeks over two hours and then Zometa as a 4-milligram and initially 8-milligram, and you will see why some of those patients were changed to 4 milligrams, every three to four weeks initially over five minutes and amended to increase the infusion time to fifteen minutes, and you will see the reasons for that momentarily.

The duration of the study was one month beyond the dosing regimen; that is, thirteen months. Patients during the trial also received

oral vitamin D and calcium daily. This was to reduce the incidence of hypocalcemia which can occur with bisphosphonate use and, indeed, in this study, those patients receiving pamidronate had a lower incidence of hypocalcemia than that that had been observed in the trials previously presented by Dr. Coleman.

A second reason for using these two medications in these patients was to reduce the potential for microfractures which can occur in animals as a result of bisphosphonate use with increases in parathyroid hormone. This has not been observed clinically, but it is a potential reason to use vitamin D and calcium as well.

[Slide.]

The primary objective of the trial is shown here. It was to demonstrate the efficacy of Zometa through the noninferiority comparison to pamidronate for the treatment of bone metastases. In this trial, a margin of 8 percent with two-sided, 95-percent, confidence intervals was used based on the results of the prior trials that Dr. Coleman presented comparing pamidronate to placebo in breast-cancer patients and myeloma patients with lytic bone disease.

We also wanted to demonstrate that the safety profile of this new bisphosphonate given chronically was comparable to chronic-used pamidronate.

[Slide.]

The primary study endpoint is shown here. It was to determine the proportion or the percent of patients experiencing at least one skeletal-related event not counting hypercalcemia of malignancy as an event for this primary endpoint.

[Slide.]

A number of secondary endpoints were also analyzed including time to first skeletal-related event, the skeletal morbidity rate, and Andersen-Gill multiple-event analysis which I will describe momentarily. In addition, the time to first skeletal-related event, skeletal morbidity rate and the number of patients experiencing any skeletal event was also determined, this time counting hypercalcemia of malignancy as a skeletal event.

The pain and analgesic scores were analyzed, a bone-lesion response as well. The time to the progression of the patient's overall disease as well as progression of their bony metastasis. Then safety was analyzed including an

analysis of survival. Importantly, beyond the thirteen months of the trial, an additional six months of safety data is available and will be presented for overall survival as well as changes in serum creatinine in these patients.

[Slide.]

The definition of a skeletal-related event is similar to that that was employed in the prior trials comparing pamidronate to placebo in breast and myeloma defined as the development of any new pathological fracture, the development of spinal-cord compression, the requirement for radiation therapy for either bone pain or to treat actual or impending pathological fractures or spinal-cord compression, surgery to bone and, as mentioned previously in some of the analyses, hypercalcemia of malignancy of defined as an event.

[Slide.]

The preplanned analysis from this trial was to determine, first of all, the proportion or the percent of patients with at least one skeletal event. This was defined as the number of patients with at least one skeletal event divided by the number of patients in that treatment group. The time to first skeletal-related event was defined as

the time the patient was randomized to the development of the first skeletal event and this was determined in days.

The skeletal morbidity rate looks at the number of events over time; that is, the number of skeletal events divided by the time the patient is on trial determined in years. The Anderson-Gill method allows one to analyze multiple events over time and it uses a more general model and takes into account not only the time of the number of events in a given period of time but the time between events as well and, thus, is a more robust analysis of multiple events over time in a given patient.

[Slide.]

The history of the trial is shown here. The initial design was to employ two doses of Zometa, either 4 or 8 milligrams, initially given over five minutes versus standard-dose pamidronate as a 90-milligram infusion given over two hours every three to four weeks for twelve months. In June of 1999, because of concerns of changes in creatinine in patients receiving Zometa, the infusion time for Zometa was increased from five to fifteen minutes.

In order to assure that was occurring, the infusion volume was also increased from 50 milliliters to 100 milliliters. The following year, in June of 2000, a second renal amendment was made because of continuing concerns in the 8-milligram dose of changes in creatinine, so all those patients subsequently received 4 milligrams and subsequently will be known as the 8/4 milligram group.

In addition, renal-function monitoring was begun so that, prior to each dose of Zometa within a two-week period of time, the serum creatinine was checked. A statistical amendment was also made because of the mix in the 8-milligram dose group so that the primary efficacy analysis was based on comparing Zometa at 4 milligrams versus pamidronate at 90 milligrams.

[Slide.]

The trial started in, as you see, the fall of 1998 and concluded approximately one year ago. Approximately half of the 1648 patients were accrued prior to the change in the infusion time from five to fifteen minutes and, indeed, nearly half of these patients only received 8 milligrams during the entire trial in the 8-milligram dosing

group.

The rest of the patients were accrued during the subsequent six-month period of time, about half of the patients. As you see, in June of 2000, a second renal amendment was made to change 8-milligram dosing patients to only receive 4. In fact, those patients who were actually entered after renal amendment 1, about a quarter of those patients only received the 8-milligram dose.

The rest of the trial was completed so that the last study visit occurred approximately one year ago.

[Slide.]

The demographics and prognostic factors among the approximately 1650 patients on this trial are shown here. One can see that the mean age was in the upper 50s. As you would guess, given that this involved a lot of breast-cancer patients, about 80 percent of the patients entered were female.

About 85 percent were Caucasian. The performance status in most cases was 0 or 1. There was an approximately equal distribution of patients who had breast cancer with metastatic bone disease who were on chemotherapy, hormonal therapy as well

as those patients with myeloma who had at least one lytic lesion. So, similar numbers of patients and similar numbers in each arm.

[Slide.]

As one can see here, the number of patients who were able to complete the study therapy through twelve months of treatment and additional months of follow up was about 60 percent and there was an equal distribution in those receiving either 4 or 8/4 Zometa versus pamidronate at 90 milligrams.

[Slide.]

The reasons for early discontinuation amongst approximately the 40 percent of patients who did not complete the study, as you would probably guess, death occurring in about 10 to 11 percent of patients and a similar proportion throughout all three arms.

Adverse events also occurring with a similar proportion amongst patients on Zometa 4, 8/4 or pamidronate at 90. Withdrawal of consent, a similar proportion. And the other causes for early discontinuation, again, nothing stands out. Small numbers and not much difference between the arms.

[Slide.]

The primary endpoint results are shown here. We are looking at the percentage of patients who had at least one skeletal event by thirteen months; that is, twelve months of treatment, an additional month of follow up. As one can see from the data, the percentage of patients having at least one skeletal event by this time point is quite similar across all three arms approximating 45 percent.

The red is Zometa at 4 milligrams, Zometa 8/4 is the blue, and the purple, here, is the pamidronate arm. Importantly, as one can also see, the Zometa at 4, and well remembering many in the 8/4 group only received 8, the percentage of patients having an event is quite similar in both of these two arms.

Now, comparison of the data shows that, indeed, the primary endpoint comparing Zometa at 4 versus pamidronate at 90, within the 95 percent confidence interval, remembering what told I said earlier, we are looking for an 8 percent margin, we can see here that Zometa may be as much as 7.9 percent better than pamidronate and as worse as 3.7 percent inferior. Indeed, this is well within the 8 percent mark that we looked at as our primary

endpoint in the trial.

Now, in order to clarify these issues better in terms of interpreting a noninferiority trial, from the statistical perspective, I now want to bring up Dr. Paul Gallo from Novartis Biostatistics.

DR. GALLO: Good morning.

[Slide.]

I would like to very briefly discuss some issues in noninferiority trials which is a very complex and quickly evolving area and their implications for the interpretation of the data that you have just seen.

A basic rationale for a noninferiority trial is that if we can show sufficient comparability between a new treatment and a standard treatment and use historical information that demonstrated how superior that standard is relative to placebo, then we can infer that the new treatment would have beaten placebo had there been a placebo arm in the current trial.

In this case, the relevant historical information comes from the pamidronate registration trials 218 and 19. I will point to this screen to the extent that I am able. I am going to summarize

an analysis that was done by the FDA statistical reviewer and was included in the briefing document.

In designing study 010, we had actually used a slightly different analysis, but the results are not practically different so I will just illustrate with this analysis to try to keep things a little bit simpler.

In a combined analysis of data from these trials, we can see that pamidronate had 13 percent fewer events than placebo and the lower limit for the magnitude of benefit was 7.3 percent. By recent conventional practice if, in the current study, we can exclude the possibility that Zometa is 7.3 percent worse than pamidronate, then we can claim that Zometa is effective. The number, 7.3, would be called the noninferiority margin. It is the potential disadvantage of Zometa that we have to disprove.

Again, we had done a slightly different analysis that led to the 8 percent margin in the protocol that was previously mentioned by Dr. Berenson.

This is a graphical illustration of what I have just described, an estimated advantage for pamidronate relative to placebo of 13.1 percent and

its confidence limits.

Recently, FDA personnel have proposed that it may be appropriately conservative to consider using an even smaller margin, in particular, half of the lower confidence limit. The rationale is that the current practice makes a constancy assumption, namely that the standard is equally effective in the current trial as it was in the historical trials. In practice, we can't guarantee that there are not subtle differences between the historical and current trials so that the standard possibly might not be as effective in the current trial.

Achieving a stricter noninferiority criterion would provide more assurance that an effect is real, even allowing for some violation of the constancy assumption. In our current case, the conservative criterion would be a margin equal to half of 7.3 percent, or 3.65 percent.

Now we look at the protocol 010 data, specifically the primary 4-milligram dose results and tie it together with the historical data by lining up the pamidronate effect. We see a 2 percent difference advantage for Zometa with a confidence limit that, in a worse case, goes as far

as a 3.7 percent advantage for pamidronate.

We can see that the conventional standard of excluding 7.3 percent is safely reached. In fact, these results just about achieve the proposed conservative standard even though the trial was not designed to be powered for such a standard which was really not in existence at that time.

So this provides somewhat of a higher level of comfort that the Zometa effect is real even allowing for the possibility that, for some reason, pamidronate might not be quite as effective here as it was in the historical trials.

So, to summarize, that is the evidence for the effectiveness of Zometa in this trial. We estimate from the data that Zometa is just a bit better than pamidronate and we know, from historical trials, that pamidronate seems to be quite a bit better than placebo and, in a worse case, both for Zometa and for pamidronate, the confidence intervals don't overlap.

Allowing for some violation of the constancy assumption by using the newer conservative standard, they still essentially don't overlap.

Now I will turn things back to Dr.

Berenson to continue with the presentation of the trial results.

DR. BERENSON: Thank you.

[Slide.]

I will continue to present the results from the trial. As you see here, we are looking at the specific types of skeletal events that occur during the trial and the proportions, actually, are quite consistent to what we observed from our earlier trials comparing pamidronate to placebo.

Indeed, fracture and radiotherapy to bone are the most frequent events. As you see here, looking at all four types of events, the proportion of patients having an event are quite similar in the pamidronate, the Zometa 4 and 8/4 group with the exception there are a smaller proportion of patients who receive Zometa at 4 milligrams who are actually experiencing the requirement for radiotherapy to bone but the 8/4 group looks a lot like pamidronate here.

[Slide.]

Indeed, the time to first skeletal-related event, a secondary endpoint in the trial, as you can see, these three curves are quite superimposable upon one another; that is, the time

to first event here is approximately one year in the Zometa 4, the 8/4 as well as the pamidronate arm and, as you see, the hazard ratios here are slightly less than 1, but do cross 1.

[Slide.]

When one looks at the number of skeletal events per year, the MSR, or skeletal morbidity rate, the red, again, is Zometa. The blue is Zometa 8/4 and the purple is pamidronate 90. The number of events per year is about 1 in the two Zometa groups, a little higher with pamidronate at 1.4 but this is not significantly different, again quite equivalent across these three arms in terms of number of events per year.

[Slide.]

Now, as I mentioned earlier, another type of analysis was done to look at the number of events per year, not just time to first event or proportional analysis of a single event. This analyzes the type to each count in skeletal-related event and, therefore, takes into account the interval between subsequent skeletal-related events in addition to just the time to the first event or the number of events over time as the SMR has done.

So we believe this is a more robust

analysis. As you can see from the hazard ratios here, which are less than 1, actually, the relative reduction or benefit in Zometa is in the range of 9 to 11 percent here in terms of the Andersen-Gill analysis. But, again, these do cross 1 but certainly suggest equivalence of pamidronate to Zometa not only in terms of time to first event and number of events per year, but multiple events over time as well.

[Slide.]

This slide is actually not in the handout for those of you who are off-site, Drs. Taylor, Albain and Kelsen, but we wanted to include it. This is an exploratory analysis to determine the proportion of breast-cancer patients who had an SRE based on the type of bone lesion they had at the time of study entry.

So those patients who had lytic bone disease had at least one lytic lesion. The blastic group only contained blastic lesions and those that could not be placed in either group were considered other.

As you see, in the lytic group, the red bar, again, Zometa at 4, and the blue bar, Zometa 8/4, the number of patients having at least one

event is actually less than in pamidronate. In the middle of the other group, there is a trend in the other direction. The pamidronate is slightly less than the other two groups.

On the right side, the blastic group, although the Zometa 4 is lower, the Zometa 8/4 looks quite similar to pamidronate. So I think it is very difficult to conclude from this single slide whether the drug works, as you well could guess, in blastic disease because the comparator here is pamidronate and we have not previously considered pamidronate in patients with blastic disease from the trials in the mid-90's. I will leave that for subsequent discussion, but I did want to show that slide.

[Slide.]

Looking at disease and quality-of-life-related endpoints, I will just summarize and I will show you some of the data. That was very comparable disease and quality-of-life-related measures and changes that were demonstrated in the two Zometa arms compared to the pamidronate arm; that is, the time to progression of bone metastasis, the time to progression of any type of malignant process going on in the patients, the

pain analgesic score changes during the trial, changes in both ECOG performance status and the FACT-G global quality-of-life were quite similar across these three arms.

[Slide.]

Now, first looking at the data for disease-related endpoints here, in the top part here, we are looking at the time to the progression of the bone disease measured in days. You can see, it is quite similar across all three arms approximating six months. Now, secondly, looking at the time to the progression of the patient's malignancy, again, the numbers are quite similar although slightly shorter for pamidronate but reassuredly show in terms of the two Zometa arms.

The Zometa, it looks quite similar. It certainly doesn't look worse than pamidronate in terms of the progression of the patient's underlying malignancy.

[Slide.]

Here we are showing the data for quality-of-life endpoints and I will summarize by telling you that brief pain inventory score changes, analgesic scores, ECOG performance changes, FACT-G total-score changes and, again, here we are looking

at the change from the baseline to either end of study or last measurement, were not significantly different from Zometa at 4, Zometa at 8/4, compared to pamidronate although those patients, over time, in terms of pain, did improve pain within each arm, just not different between the arms.

[Slide.]

So here is a summary of the efficacy data from the trial. On the left side, we are looking, again, at the percent of patients who had at least one skeletal event by thirteen months, twelve months of therapy, one month of additional follow up, and the numbers are strikingly quite similar, 44, 46 and 46.

The time to first skeletal-related event, hazard ratio less than 1, crosses 1, again consistent with equivalence of this drug in terms of efficacy to standard-dose pamidronate. The mean SMR--as I mentioned earlier, the SMRs were around 1 for the two Zometa arms, slightly higher in the pamidronate arm, 1.4, but not significantly different.

Looking at multiple events over time in a little different matter, as I mentioned earlier, by Andersen-Gill analysis, the hazard ratios, in fact,

are less than 1, again cross 1. So, overall, the results of this trial in terms of efficacy certainly suggest comparable efficacy of this new drug to pamidronate in reducing skeletal complications in these patients.

[Slide.]

Now let's turn our attention to the safety data from this trial. The primary cause of death during the trial or within one month after study drug termination is shown here. As you could guess, the most common cause, of course, would be the underlying malignancy in approximately 8 to 10 percent of patients throughout all three of these arms.

Other causes which were less common, including respiratory, cardiac and infectious causes, certainly are similar across all three arms and the other less common causes, as you can see, the numbers quite small and quite similar across three arms, very reassuring.

[Slide.]

Now, overall survival was obviously looked at as well. As you can see, in this trial, in those patients again with breast cancer metastatic to bone and myeloma with at least one lytic lesion,

the survival was approximately 800 days in all three arms, strikingly similar in the Zometa 4, 8/4 and pamidronate arms with p-values that are very high and much above 0.05.

[Slide.]

The incidence of adverse events that occurred in at least 15 percent of patients in one of the arms is shown here regardless of whether we believed it was related to the study drug. You see a lot of white here indicating that there were very similar proportions of patients in all three arms having these events with the exception of the yellow, pyrexia, a known side effect with the first or second administration of bisphosphonates, about 5 percent more common in the Zometa arms and, indeed, anorexia, really for unknown reasons, a little bit more than 5 percent than the pamidronate in the 4-milligram arm. But there are a lot, as you see, of adverse events we looked at.

[Slide.]

Now, importantly, the incidence of anemia has been shown to be higher with chronic administration of pamidronate in the previously done trials comparing pamidronate to placebo in breast-cancer on chemotherapy and myeloma patients

with at least one lytic lesion.

Although, there was some incidence of anemia, it was less than 6 percent in all treatment groups and was not different between the treatment groups as well. Of probably more importance, the use of packed red blood-cell transfusions and exogenous erythropoietin support was not different between the treatment arms as well.

Electrolyte and mineral adverse events, mentioned previously in Dr. Coleman's talk which occurs with pamidronate occasionally, this incidence was quite uncommon in all treatment groups. The most common events with the Zometa at the 4-milligram dose were hypophosphatemia, low potassium or high potassium, but these were uncommon.

[Slide.]

Now, the definition of serum creatinine used to monitor these patients following renal amendment 2 was a serum creatinine that was normal at baseline and then increased by 0.5 milligrams per deciliter. A serum creatinine that was abnormal at baseline and increased by more than 1 milligram per deciliter or a doubling of serum creatinine from the number that was available at

study entry.

If the serum creatinine was increased by any of these three determinations, it was decided to hold the dose until it returned to 10 percent of the baseline serum level.

[Slide.]

This is a rather complex slide but an important one. Turning our attention, first of all, to the top half of the slide, this is the number of patients who had no increase of serum creatinine and, again, the definitions I showed you in the previous slide, before we changed the infusion time from five to fifteen minutes.

The purple line represents patients on pamidronate. The two Zometa curves in red and light blue, as you can see, are lower lines suggesting that, indeed, before the amendment change was made, a slowing of infusion time, there was an increased risk of creatinines going up in patients on Zometa in the 4 or 8/4 group.

Following the amendment change, shown in the bottom half of the slide, and, again, about half of the patients accrued at that time, one can see a disappearance of the increased risk of renal problems or creatinine rises in those patients who

were receiving Zometa at 4 over fifteen minutes; that is, the dark red and the purple curves are superimposable, hazard ratio there at 1.012.

But we continue to observe problems in the 8-milligram dose when given over fifteen minutes in the light blue with a hazard ratio over 2 and a quite significant p-value suggesting continued problems. Importantly, as I mentioned earlier, nearly half of the patients who were on the 8-milligram dose prior to the fifteen-minute infusion time change only received that dose, about 21 percent of patients following that change.

[Slide.]

Now, let's look at the data globally in terms of significant NCI grade 3 and 4 serum creatinine changes. After the fifteen-minute amendment was changed, only those patients enrolled, again that was about half of the 1648, 803, and one can see grade 3 problems only in one patient at Zometa at 4, no grade 4s, and, as you can see, slightly more in the Zometa 8/4s at six grade 3s and one grade 4, again, necessitating the change in those patients from 8 to 4.

In the pamidronate, in fact, there were more events here of grade 3 and grade 4 than Zometa

at 4.

[Slide.]

So the safety summary that I have just outlined tells that when you give Zometa at a 4-milligram i.v. dose over fifteen minutes every three to four weeks, the safety profile, including changes in creatinine, is quite comparable to intravenously administered pamidronate at 90 milligrams over two hours.

[Slide.]

Indeed, an overall summary of this trial would tell us that Zometa at 4 milligrams over fifteen minutes given every three to four weeks demonstrates comparable safety and efficacy as noninferiority design in this trial to standard dose pamidronate at 90 milligrams over 120 minutes in treating bone metastasis of all types in patients in breast cancer, in lytic bone disease, in multiple myeloma.

DR. NERENSTONE: Thank you very much. We are going to go right to the FDA presentation for review of the study 010. Then we are going to leave the clarifying questions to both the sponsor and the FDA until after the FDA presentation.

FDA Presentation

Zometa in Breast Cancer and Multiple Myeloma
(Study 010)

DR. WILLIAMS: Dr. Nerenstone, members of ODAC, it is my pleasure to begin the FDA presentation of this application.

[Slide.]

I want to break from protocol a little. You are welcome to interrupt me if I am on wrong slide. Otherwise, we will wait until the end.

[Slide.]

First, I would like to recognize the FDA review team. The FDA clinical review team worked hard to review this large complicated application. This slide recognizes the members of that team. Debra Vause led us as project manager. Five medical and statistical reviewers helped prepare the information for this meeting. Medical reviewers included myself for study 010, Dr. Amna Ibrahim for studies 011 and 039, Dr. Nancy Scher for the safety data from these studies and Dr. Richard Pazdur, our Division Director.

The statistical review of study 010 was performed by Dr. Ning Li for study 010. For 011 and 039 was Dr. Raji Sridhara. And the statistical team leader is Dr. Gang Chen. All of the reviewers

will be available for questions and discussion.

[Slide.]

This is the outline of my presentation. First, I will present an overview and then a regulatory framework followed by discussion of the FDA findings from study 010 and myeloma and breast cancer. The latter will include a discussion of the noninferiority trial design, results and examination of assumptions.

[Slide.]

As a reminder, this is the proposed Zometa indication; treatment of osteolytic, osteoblastic and mixed bone metastases of solid tumors and osteolytic of multiple myeloma. These are in conjunction with standard antineoplastic therapy.

[Slide.]

The FDA reviews the Zometa from a regulatory perspective as well as from a scientific perspective. The FDA requirement to demonstrate efficacy dates to a 1962 amendment to the Federal Food, Drug and Cosmetic Act which required substantial evidence of efficacy from adequate and well-controlled investigations.

Usually, this means evidence from multiple clinical trials but very impressive and robust

results from a single multicenter trial has sometimes been accepted. An important question you will be considering during your deliberations will be whether these trials meet the regulatory efficacy requirement.

You will be asked this for each of the different indications that correspond to the different trials. You might find that one of the trials is so impressive that it supports approval withput any support from the other trials or you may find that, while a single trial is not convincing enough to stand alone, you find the results of one of the other trials to be supportive also.

It is a matter of both science and of judgment whether the results of the different trials support each other. This is a fitting topic for ODAC and we invite your advice.

[Slide.]

At the planning stage, both FDA and Novartis assumed that some sharing of information between tumor types was reasonable. For example, breast cancer and myeloma were combined in a single study. For each indication, only single studies were planned. Finally, multiple different solid-tumor types

were lumped together in the single study 011.

Of course, these general assumptions were made without having the results in hand. The questions before ODAC concern specifics. Now, with the result in hand, there may be unanticipated questions. This often seems to happen in clinical trials in the real world. So we need your advice whether these assumptions are still reasonable in light of the clinical-trial data.

[Slide.]

In the next two slides, I want to discuss the skeletal-related event analyses used in these studies. Evaluating efficacy by measuring cancer-patient morbidity is difficult and there is no perfect endpoint. Patients suffering from cancer often drop out early from studies either from death, side effects of treatment of from other cancer problems not captured by the endpoint.

Historically, in evaluating bisphosphonate treatment of cancer metastatic to bone, FDA has emphasized two very closely related endpoints; first, the proportion of patients entering the study who have a documented event and, second, the time to skeletal-related event.

In studies of bisphosphonate, the results from these two analyses usually go hand in hand and this should not be surprising. Both use exactly the same skeletal events. The first analysis describes the number of patients with at least one event and the second uses the additional information of event timing.

During FDA analysis of these studies, questions arose regarding which of the two different endpoints was preferred.

[Slide.]

However, both endpoints share serious problems. That problem is dropouts. Some patients who drop out may subsequently have an event and this is not counted. This would lead to an underestimation of the event frequency in the proportions analysis.

Furthermore, patients may drop out because of symptoms of an impending event and that event is not documented as such. This would lead to a phenomenon known as informative censoring, something that would violate assumptions of the time-to-event analysis. This analysis assumes that censoring occurs in a random manner.

These analyses share the problem of

competing risks, simultaneous risk of cancer-related problems such as death and the risk of having a skeletal event. With both endpoints, there is likely to be bias in estimating the true effect of the drug. This bias could affect how accurately we describe the benefit of the drug but this bias should apply equally and in the same direction to both arms.

Because this study is blinded, neither analysis should introduce bias between the study arms. So a significant p-value for either endpoint might be viewed as valid evidence that efficacy has been demonstrated. I am sure that ODAC's Dr. George and the FDA statisticians will be glad to discuss this point further during this afternoon's discussion.

So I believe we should view these two closely-related endpoints with a bit more flexibility than we might otherwise in evaluating primary and secondary endpoints. Novartis' prespecified endpoint was the proportion of patients having an event. The FDA's statisticians preferred analysis, this time to SRE.

As you have observed in these trials, results were sometimes statistically significant

for one endpoint but not for the other.

[Slide.]

Each of the clinical trials raised one or more important questions which I will summarize in the following three slides. For study 010 in breast cancer and myeloma, we note that it was a single study of noninferiority design. Due to the inherent weakness of noninferiority studies, we usually expect results from two such studies or additional evidence from studies of a different design.

The question for ODAC, do the totality of the data in the NDA provide support for this indication. We believe they do and we invite your comments.

[Slide.]

In prostate cancer, the 4-milligram Zometa arm shows convincing results for both the primary and secondary event endpoints. The 8-milligram arm shows no statistical difference from placebo. Two questions arise; first, considering both arms of the study, how convincing are these data that Zometa, 4 milligrams, is effective?

Second, prostate cancer produces blastic bone metastasis. In considering the efficacy of

Zometa in prostate cancer, is it reasonable to also consider evidence of Zometa efficacy from studies of lytic bone metastases from other cancers?

Finally, after you consider all of the evidence in the NDA, we will ask you whether the regulatory efficacy requirement has been satisfied for Zometa and prostate cancer; that is, is there substantial evidence of efficacy from adequate and well-controlled investigations?

[Slide.]

In patients with other solid tumors, the 4-milligram arm was statistically better than placebo in time to skeletal-related event but not by the proportions analysis. The 8-milligram Zometa arm was statistically better than placebo in both analyses. FDA believes the data are convincing, that the population studied in this trial received a benefit from Zometa.

However, the population studied was heterogeneous composed of patients with many different tumor types. The question we want you to consider is whether these data support approval for treatment of all individual patients with all types of other solid tumors.

[Slide.]

Now, we will turn to study 010. As you have heard, study 010 was an international multicenter stratified double-blind study that randomized patients to Zometa 4 milligrams, Zometa 8 milligrams or Aredia 90 milligrams i.v. every three to four weeks for twelve months.

Randomization was stratified by center and three disease strata; myeloma, breast cancer treated with hormones and breast cancer treated with chemotherapy. In this trial, the efficacy of Zometa was determined by a noninferiority comparison to Aredia.

[Slide.]

First, a few comments about design. First, the design of this study assumes that data from the bisphosphonate efficacy in bone metastases and myeloma and breast cancer can be combined and analyzed together.

Then a few comments about the inferiority design. Here are listed several different points or several different steps in the noninferiority analysis. I think Novartis did a nice job of presenting that. First, you estimate the historical Aredia effect size versus placebo. Then you compare Zometa and Aredia in the current study.

You determine Zometa efficacy by showing that a reasonable fraction of the Aredia effect size is proven for Zometa using statistical methodology. Finally, you evaluate the constancy assumption.

There is much discussion and research regarding the best methodology for performing noninferiority analyses. In this case, because only a single noninferiority trial was submitted, FDA used a conservative method, the two 95 percent confidence interval method which I will describe. I think, again, Novartis has touched on this so I will be brief.

[Slide.]

As you have seen, the slide summarized the efficacy of Aredia showing the 13.1 percent difference from historical trials. In the submission, Novartis had centered on the 13.1 percent as the effect size. In the FDA's more conservative analysis, we have used the 7.3 percent lower confidence interval.

[Slide.]

Then, there is a comparison between Aredia and Zometa, as you see, a 44 percent event rate on the Zometa arm versus 46 percent on the Aredia arm.

[Slide.]

Although the estimate from these data favors Aredia by 2 percent, again, the method used a conservative limit of the confidence interval to estimate the Zometa effect at 3.7 percent. By the FDA analysis, using the effect size of historical estimate of 7.3 percent and the worst-case estimate of Zometa effect at 3.7 percent, we calculated 49 percent retention of the Aredia effect versus placebo in sort of a worst-case analysis.

[Slide.]

A critical assumption of making conclusions from noninferiority trials is this constancy assumption. This requires a determination that active control drug, Aredia, would have shown efficacy versus placebo in the current clinical-trial setting.

Potential problems that could challenge this constancy assumption include different study populations in the historical study compared to the current study, changes in supportive care and also study conduct could affect this assumption. Sloppy trial conduct could obscure differences and make it easier to win than a noninferiority analysis.

[Slide.]

Important differences were found between

the current and historical studies. Compared to the Aredia versus placebo studies, more patients on study 010 had a short time since diagnosis of bone metastases. More patients had a history of a previous skeletal-related events. In breast cancer, more patients had no lytic bone lesions.

[Slide.]

So FDA used a couple of approaches to evaluate the importance of these historical differences. First, retrospective analysis of the estimates of Aredia versus placebo data showed that the Aredia effect appeared even greater in patients with a short time since diagnosis of bone metastases and in patients with a history of previous skeletal-related event.

Therefore, enrichment of the study population with these patients should, if anything, increase the sensitivity of the study.

[Slide.]

The question of whether the active control Aredia is effective in breast-cancer patients without lytic lesions, however, cannot be directly examined in by an historical Aredia versus placebo study because only patients with lytic lesions were entered. One can examine Zometa efficacy in the

subgroup of study 010 who had lytic disease. Such a subgroup analysis of study 010 comparing Zometa versus Aredia and breast-cancer patients with lytic bone lesions did not suggest a lack of Zometa efficacy here.

As this slide shows, it suggested a noninferiority trend in favor of Zometa.

[Slide.]

Another concern was that Aredia might have been effective in decreasing certain types of skeletal-related events such as fractures but that the current study had few such events. This possibility was evaluated and the types of skeletal-related events found most commonly in the historical Aredia trials were similar to those seen in study 010. Most were fractures and radiation therapy to bone.

[Slide.]

So these are the FDA conclusions from the study. Study 010 is a single study of noninferiority design demonstrating efficacy of Zometa for patients with bone lesions of myeloma and breast cancer. We believe other data from studies 011 and 039 are supportive and they collectively meet the regulatory requirement for

substantial evidence of efficacy for well-controlled investigations for the treatment of myeloma and breast cancer.

We look forward to your discussion and your advice.

Than you. Both the medical reviewers and the statistical group will be available for clarifying questions in the table along with the company and then, this afternoon, we will also be here for the discussion.

DR. TEMPLETON-SOMERS: We would like to check and see if Dr. Albain and Dr. Kelsen and maybe Dr. Taylor are on line.

DR. KELSEN: David Kelsen in New York.

DR. TEMPLETON-SOMERS: Kathy, are you there, too?

DR. ALBAIN: Yes; I am here.

DR. TEMPLETON-SOMERS: Is there any chance that Sarah made it through the snow storm?

DR. TAYLOR: I'm here.

DR. TEMPLETON-SOMERS: Good. We are glad to see you. How is the weather there?

DR. TAYLOR: There are a lot of trees down and a lot of ice.

DR. NERENSTONE: Now we see you, Sarah.

Welcome. We were afraid we wouldn't get to you today, or you wouldn't get to us.

I am going to open in now for questions from the committee.

Questions from the Committee

DR. NERENSTONE: I want to remind everybody that we really want to stay focused on just factual questions and don't want to open up for discussion. We will have lots of time for that later.

Questions from the committee for either Novartis or FDA? Dr. George?

DR. GEORGE: I have a question about the original design, the rationale behind having two doses and what the objective of the study was of that. Was there a feeling that there might be a dose-response kind of effect or was it simply to have two different doses, both of which would be compared independently to the placebo--well, all of these studies had the same question.

DR. NERENSTONE: Would whoever comes up to the podium please identify himself.

DR. SEAMAN: Good morning. I am Dr. John Seaman from Novartis. I worked on all the Aredia submissions and also the Zometa submission. Going

back to the historical reason for the 8-milligram and the 4-milligram being included in this trial, it was basically done because, when we did our phase I trial, we saw markers of bone resorption being suppressed to a great extent with the 8-milligram dose versus the 4.

We had gone all the way up to a 16-milligram dose and saw no increase in the suppression so we felt that, using that surrogate marker as and endpoint, we should go a bit higher to see if we had better efficacy.

Unfortunately, we didn't have the data from the hypercalcemia trials to show there was an equivalent efficacy in terms of 8 and 4 when we got that trial started.

DR. NERENSTONE: Dr. George

DR. GEORGE: Just a quick follow up. The reason I am asking is to try to determine what your mind set was. Did you anticipate that you could have had a situation where there is a reversal; that is, that the 4 looks effective not the 8 and vice-versa. How would you have interpreted that? In other words, were you looking at a dose-response kind of thing or were you really just going to compare them as if they are two treatments, two

placebo, and see--

DR. SEAMAN: We were looking to see if we were going to get a dose response, we would have a better response rate.

DR. NERENSTONE: Dr. Raghavan?

DR. RAGHAVAN: I really do understand all the flaws of retrospective subset analysis but one of the things that has puzzled me is some of the inconsistencies between the 4 and the 8/4. So, recognizing all the flaws of doing a subset analysis post hoc, do you have any information you can share with us about the absolutely pure 8-milligram group dissecting out the post-fiddling dose reduction time change? Do you have any data that give the same sort of endpoints that you looked at the for the global group taking out just the 8-milligram doses, pure 8-milligram doses?

DR. SEAMAN: Unfortunately, we don't have any 8-milligram-dose-alone efficacy.

DR. NERENSTONE: I have a question along those same lines. It seems to me that, according to the presentation that the 8-milligram dose had a higher incidence of renal problems and, therefore, the doses were held until the creatinine came back down to normal.

Can you give us a feeling for how many doses were held and how long and is there a possibility that what happened is that, instead of 8-milligram dosing every three to four weeks, you had a number of patients who got 8-milligram dosing every six to eight weeks?

I agree with Derek that there is some inconsistency in the data and I was just wondering if you have any other thoughts about that?

DR. SEAMAN: Why don't I turn this over to Dr. Raimund Hirschberg who is from UCLA and was a member of our renal advisory board that actually looked at every piece of this data and let him answer that for you.

DR. HIRSCHBERG: At the time, in June of 2000 when this second amendment which included this creatinine sort of flag point, at this same time, the 8-milligram dose was discontinued so this could not have kicked in with the 8-milligram dose. It excluded each other.

DR. TEMPLE: I didn't see a noninferiority analysis of the 8-milligram, 8/4, dose. Did you do that? I mean, in some sense, it is a replication of the other or could be taken as. Obviously, we know the rates were equal, but did you do a similar

analysis?

DR. SEAMAN: I will have Dr. Bee-Lian Chen, our statistician, answer that. We did do a 8/4 analysis. This is Dr. Bee-Lian Chen from Novartis.

DR. CHEN: My name is Bee-Lian Chen. I am the project statistician for the project. I may answer the question too quick in terms of noninferiority. It is based on extensive analysis as done by FDA and internally by Novartis. But when we performed the analysis for the study report, we pretty much paralleled the comparison, the 4-milligram versus Aredia 90 milligrams and 8-milligram versus Aredia 90 milligrams.

Basically, we have the confidence interval based on the study 010 results. But, in terms of extensive analysis performed with the noninferiority details, we didn't do that.

DR. TEMPLE: The main result you report is that you have pretty close to 50 percent retention of a conservatively estimated effect of pamidronate. It certainly is conservative to say 8 percent is the lower bound. That is the lower bound of the 95 percent confidence interval. That is not the typical result. That is an extremely

low result for pamidronate.

So, granting that it is conservative, you then do your analysis and you show the difference between the two treatments has a worst-case bound of almost the same as half of that effect. Fine. So you must have some idea what the upper bound for the 8/4 group is and be able to say with some idea what percent retention of the pamidronate effect you have in that group.

DR. CHEN: The FDA statistician--

DR. TEMPLE: Or we do; right.

DR. NERENSTONE: Dr. Li of FDA?

DR. LI: Ning Li, FDA. Actually we did the 930 analysis for the 8-milligram arm under--the committee members who got the FDA briefing package can find the analysis on page 68, in the statistical review.

Essentially, the result is comparable to the 4 milligrams for study 010. The only difference is the percentage of retention is lower. It is about 20, 20.5, percent rather than the 49 percent as in the 4-milligram arm, so still demonstrating the 20 percent efficacy compared to placebo according to our analysis.

DR. TEMPLE: Can I just make one

observation? Dr. Gallo said that the reason that you do this 50 percent is to support the constancy assumption. This will be discussed later but that is incorrect. You evaluate the constancy on its own. You make your best guess. There is no way to really do it.

The preservation of effect is a clinical judgment; that is, how much of the effect of the control agent must you have. After all, this is a situation in which you are so sure the control agent has an effect that you are not allowing yourself to use a placebo.

So we customarily ask--this is well-established--how reassured are we that the effect of the control is present. Arbitrarily, completely arbitrarily, we have often said something like 50 percent, but we don't stick to that. So it is of some interest that the second group didn't have as strong support that it retained at least 50 percent. But, again, this is a very conservative analysis and we know that. We have used much less conservative analyses and presented them to this committee.

DR. NERENSTONE: Dr. Przepiorka?

DR. PRZEPIORKA: A question about the

study population, if I can. What percentage of the patients had hypercalcemia at the time of enrollment in the study and what percentage actually received vitamin D and calcium, as Dr. Berenson indicated in one of his slides, throughout the study?

DR. SEAMAN: Can I get a little clarification what percentage in terms of entry into the trial or occurred during the course of trial?

DR. PRZEPIORKA: At the time of entry.

DR. SEAMAN: No one had hypercalcemia. That was an exclusion criteria for entering the trial and everyone was to receive calcium and oral vitamin D during the course of the trial.

DR. PRZEPIORKA: 10 percent of the patients withdraw consent. Is there any sense for why?

DR. SEAMAN: It probably has mostly to do with the patient population. We looked at that and went back and looked at our old Aredia trials and determined that basically these patients are progressing and they just don't want to come back and talk to some of our investigators, and they felt the same thing. They just withdrew consent.

They were terminal and just stopped coming. It is much higher in our subsequent trials you will see today.

DR. NERENSTONE: Dr. George

DR. GEORGE: I have a question about the constancy assumption in the 010 trial. In particular, most of what was presented--I guess all that was presented today had to do with breast cancer and myeloma sort of together, but one sort of piece of indirect evidence about the constancy assumption would be to look at the Aredia, just the proportion who had SREs historically compared to what happened in this trial.

In the myeloma group, it looked much lower in the past. The percentage of patients with SREs in the NDA studies was much lower than on the 010 trial in contrast with the breast cancer which was very similar, almost identical, in fact, remarkably similar. Do you have any explanation for this little tidbit because the issue might be, of course, that the effect on this new trial is you are doing a noninferiority to something that is not any different than placebo. Do you have any reason for that?

DR. SEAMAN: You are correct, and Dr. Dirk

Reitsma, who is a clinical research physician and has been working with me for the last fifteen years with Aredia and Zometa will answer that question.

DR. REITSMA: Good morning. My name is Dirk Reitsma. I am a research physician with Novartis Oncology Development. It is actually a very interesting observation that you brought up. It appears, as you say, in contrast to the breast-cancer trials that, in the multiple-myeloma trials, there are more events.

I will show you that.

[Slide.]

This slide shows you the proportion of patients having any SRE contrasting the previous trial in pamidronate with the multiple-myeloma patients on top, study 012, and Zometa study 010 on the bottom. The two lines to look at are the top line in the old study 012, the pamidronate 90 milligrams, and the bottom line, pamidronate 90 milligrams in study 010.

What you see is the difference at the very beginning between 010 and 025. What you also see is that these programs behave in much the same way. If you go across from three to twelve months, it is 10 to 21 to 24 to 38. In the bottom line, it is,

again, a big jump in the beginning, 25 to 40, and a leveling off of the accrual of events.

Now, that is odd and I think the clue to that is on the next slide.

[Slide.]

What you see here is the demographic and some prognostic variables, specifically age, which is the same all the way across for both trials. The old pamidronate trial is on the left and the study 010 is on the right.

If you look at the bottom line, I think that is the clue to what was happening and it was shown already by Dr. Berenson,

I believe, where you see the longer median time from diagnosis to visit 2 in the previous trial compared to now, what happened was, in the meantime, Aredia was approved for treatment. People realized that once these people had a bone disease, they needed to get treatment.

The puzzling bit about that is why would they have more fractures at that point. So the hypothesis becomes that the event rate in patients being diagnosed with multiple myeloma is initially driven by that cohort of lesions they have when they come untreated into the trial, bearing in mind

that a lot of the breast-cancer patients at that point would already have been on treatment for other metastases unlike multiple myeloma which present with bone disease.

So, if I can have the next slide.

[Slide.]

The way to look at that would be to look at time between diagnosis and getting into the trial and how that affected the event rate. Here you see, on the top again, the old pamidronate trial of multiple myeloma and, on the right, that column that says, "with pathologic fractures," you see that split out by patients that had had their diagnosis within six months and patients that had their diagnosis longer than that.

You see that it is true that those patients do, indeed, have a higher event rate with a recent diagnosis. So that would say, indeed, before the treatment kicks in and the chemotherapy, they have events. So you see, basically, the same thing in a slightly different cut of the data from the current trial 010 on the bottom of the slide.

Again, if you look across, starting at three months, you see the patients that just came into the trial had a higher rate of 21 compared to

15 if they had been diagnosed previously by which time chemotherapy would have kicked in in a lot of patients. After that, you see a fairly similar behavior in both groups.

DR. NERENSTONE: Dr. Loehrer?

DR. LOEHRER: I just have a couple of questions because I can't remember. In the original pamidronate studies, did everyone get vitamin D and calcium?

DR. SEAMAN: No. In the original pamidronate trials, not everyone got vitamin D and calcium.

DR. LOEHRER: That impact, in terms of this therapy, then, it is a couple of different variables compared to the historical controls; is that right?

DR. SEAMAN: I think it had a major impact on particularly electrolyte and mineral imbalances in terms of the amount of vitamin D and calcium that was given. It wasn't even the minimum daily requirement that we would take on a daily basis.

DR. LOEHRER: One of the things Dr. Berenson mentioned, and I kind of skipped through this and I wasn't sure, is, in the skeletal-related events, it was said, actually, that hypercalcemia

was included in terms of their criteria yet he said it was used sparingly. It is not clear how this hypercalcemia was actually included in these incidents of skeletal-related events.

DR. SEAMAN: The analysis that we have done and presented here today did not included hypercalcemia of malignancy. Either Grant or myself can answer the question regarding why we don't include it, but, in essence, we didn't include it because we know bisphosphonates work in hypercalcemia and we thought that that was not an important endpoint and not including it was probably appropriate.

DR. LOEHRER: Just two more questions. One is, there were four renal deaths in the 8-milligram dosage. Can you explain, were those part--were they drug related or incidental, do you think?

DR. SEAMAN: There were renal deaths in this trial. Mainly, they were myeloma patients. In every case, there was underlying pathophysiology and drugs that were on board that you couldn't sort out whether it was being caused by the drug or the disease.

DR. LOEHRER: Just finally, just again a

comment, on Dr. Coleman's slide because there are some people in the audience who are not necessarily sophisticated and who may be more stockholders, but when one looks at, for example, the incidence of the various malignancies on a second slide for bladder cancer, for example, one might suspect, if you would be real excited and multiple 40 percent by 582,000 and think this is how many patients are going to be candidates for receiving this drug, the fallacy of that, actually, is that, at autopsy, for example, that 40 percent of the patients have it. 8 percent of bladder cancer patients, for example, are going to survive without having metastatic disease. So, I think, just to clarify those issues. The same with the other malignancies.

DR. SEAMAN: Okay.

DR. NERENSTONE: I would like to ask Dr. Kelsen, Dr. Albain or Dr. Taylor if they have any questions for either our sponsor or the FDA.

DR. TAYLOR: I don't at this point.

DR. ALBAIN: I have a question or two. This is Kathy. I have a question regarding the systemic therapy status at the time of study entry. In particular, were these patients already on some stable type of chemotherapy or hormonal therapy or

were they newly progressing and just started on a new systemic therapy because, certainly, in breast cancer and, to some degree, in myeloma, the systemic therapy could significantly reduce skeletal-related as well as visceral events.

So, could you comment on that first and then I have a follow-up to that.

DR. SEAMAN: The answer to that first question is that patients entered the trial on appropriate antineoplastic therapy and that meant that they could have started anywhere from the last year to the last two to three weeks prior to entering the trial. So it is a whole host of patients that are coming in at a variety of times during the course of the disease.

DR. ALBAIN: Do you have any data on how often the therapy was changed during the course of the trial for each of the subsets, the chemotherapy and the hormonal subset?

DR. SEAMAN: Yes. Just a second and we will find that. Can I have this slide up? This is for multiple myeloma, how many regimen changes were done during the course of the trial.

[Slide.]

You can see that around 6 percent stayed

on the same therapy they entered and 6 percent of the patients went to greater than five changes. The vast majority had between one and two changes during the course of the study.

DR. ALBAIN: I can't read that.

DR. SEAMAN: Oh; I'm sorry. I apologize.

DR. ALBAIN: The difference between the three arms; was there any difference among the arms?

DR. SEAMAN: Not really when you look at the proportion of patients having changes in their chemotherapy in the myeloma, it is very similar depending on whether they had one, two or three changes or up to five changes.

DR. ALBAIN: Do you have this data for breast-cancer chemotherapy?

DR. SEAMAN: Yes.

[Slide.]

The next slide displayed on this slide--I know you can't see it. I apologize--the breast-cancer chemotherapy changes and the breast-cancer hormonal changes. In the course of the trial for the breast-cancer chemotherapy changes, there were no changes in terms of entering the trial, only around 1 to 3 percent of the patients.

The vast majority had one to two changes--around 30 percent had one to two changes in their chemotherapy regimen and they were equivalent across the treatment groups. In terms of their hormonal therapies, the vast majority here, in terms of changes, occurred only once. Around 40 to 50 percent of the patients had a change in their hormonal therapy during the course of the trial and twice in between, 25 and 32 percent of patients having a change in their hormonal therapy.

DR. ALBAIN: One last question. Could you comment on the study-treatment duration of twelve months. Do you have any data, perhaps not from this trial, but from the pamidronate trials on longer durations and toxicity beyond for those patients doing well at twelve months?

DR. SEAMAN: This trial was initially designed to not only have a twelve-month core in terms of looking at the overall efficacy and safety of Zometa versus pamidronate but also has an extension which will close the last patient, last visit, within the next few months and will be subject to another supplemental NDA next year for long-term data.

In the pamidronate trials, we have data up

to 24 months for breast cancer and 21 months for myeloma. There is no difference in the overall safety profiles that we could see that would occur at a later date. One of the things that was of concern, there may have been a few more renal events in the myeloma patient population in protocol 012, the original Aredia trial, but it wasn't clear to us, and still is not clear to us, if that was probably the disease and not the drug.

DR. ALBAIN: Thank you very much.

DR. NERENSTONE: Dr. Taylor, did you have a question for us?

DR. TAYLOR: Just to clarify, then, we don't really know how many patients were on second- or third-line chemotherapy when they came into the trial?

DR. SEAMAN: I don't know, at trial entry, how many were on second-line or third-line chemotherapy. I know how many changes were taking place during the course of the trial.

DR. TAYLOR: In the pamidronate data, over that two-year period, can you tell if there was continued reduction in skeletal events?

DR. SEAMAN: I'm sorry; I couldn't hear you.

DR. TAYLOR: Was there continued reduction in skeletal events over the 24-month period of time with the pamidronate?

DR. SEAMAN: Yes. In the pamidronate trials, you saw a continued effect on skeletal-related events for the 24-month breast-cancer data and the 21-month myeloma data.

DR. TAYLOR: Thank you.

DR. NERENSTONE: Dr. Przepiorka?

DR. PRZEPIORKA: The difference between the pamidronate and placebo was actually, according to the data here, somewhat smaller than at the twelve-month mark. Do you have any preliminary data from the current trial regarding time to skeletal-related events after twelve months?

DR. SEAMAN: No. That is the subject of the studies that we are closing down now in terms of the extension. We will have that data within the next year.

DR. COLEMAN: Dr. Pelusi?

DR. PELUSI: Two questions. One is, either in your historical data or in your current studies, do you see any difference in ethnic minorities in terms of response to bisphosphonates at all because it seemed like the majority of

people accrued to the current studies were mostly Caucasian patients?

DR. SEAMAN: That is even more true for the original Aredia trials but I will share with you what we have from these trials so you can make your own judgment. As you said, the sample sizes here are small.

Could I have the slide up, 43, please?

[Slide.]

As I said, the sample sizes are small in terms of other types of races, whether it be black or other, as we captured them. But you can see, in protocol 010, again with pamidronate control trial, that around 29 percent of the patients in the Zometa 4-milligram treatment arm had an SRE and around 30 percent of the pamidronate arm.

In protocol 011, around 27 percent had an SRE in the Zometa treatment arm and 33 percent in the placebo arm. More importantly, in protocol 039, the prostate-cancer patient population which has a problem in terms of the number of blacks having it and now progressive seems to be in the black patient population.

There is a 17 percentage of the patients having an SRE in the 4-milligram arm for Zometa and

a 42 percent for placebo, which is quite high. But, again, remembering the n's are small in all these trials.

DR. PELUSI: My last question would relate to your quality-of-life assessments. Were the quality-of-life assessments done in general for quality of life or was it specifically looking at quality of life as related to skeletal events?

DR. SEAMAN: Unfortunately, there are no quality-of-life tools for skeletal-related events. The ones we used were, as you saw, FACT-G and ECOG performance status. That is the best we could do at that time. There still is nothing that I am aware of.

DR. PELUSI: I don't think there is but I guess the point that I was trying to just kind of bring up to our awareness is, as we are looking at some of these endpoints, is do we really ask the question, what do these skeletal-related events do in terms of function and being able to look at what are the goals for some of the patients.

Thank you.

DR. SEAMAN: I am in agreement.

DR. NERENSTONE: Dr. Raghavan?

DR. RAGHAVAN: This is directed, actually,

to Dr. Williams. It may be that I misunderstood your statistician in the reference to pages 67 and 68. Did any of the twelve inquiring minds in your team with the n equals 300 patients that had 8 milligrams to look at the early phase of the trial? 300 patients got through the phase I part of the trial. That is not a subset selection, really, because they were just being left alone until they ran into renal problems.

It is actually kind of interesting to look at the whole global day's presentation, stuff we have had in advance, this dichotomy between 8, 8/4 and 4. It would expect, Grant, you or one of the group would have played with the numbers.

DR. WILLIAMS: Thanks. Now, who all do you include in this?

DR. RAGHAVAN: I would say the twelve inquiring minds that you listed. I wouldn't leave anybody out, so I counted very carefully.

DR. WILLIAMS: I think our approach basically was to consider that the 8-milligram arm really was an 8-milligram arm. If you start looking at the times when they were accrued and how many doses they received, there is a very small number of doses and many patients received only 8

milligrams.

So, from an efficacy standpoint, I think it is a complete study. Dr. Ibrahim has done analyses in her studies and in mine that they basically received the same numbers of doses of something and most of them were 8 milligrams. We looked carefully to see if we could find the evidence that there was a problem with that arm and we just didn't see it.

I think if you accept the results, I think we would feel that they would have to be more by chance than anything else.

DR. SRIDHARA: I am Rajeshwari Sridhara. The study was reviewed by Ling Li, but if you refer to the statistical review on page 19, you get some sense of what was going on. As Grant said, it was not possible for us to look at how many doses each received or whether they received exactly 8 or 4, but it tells you, over a period of time, how the events were occurring. So that gives you some sense of what was happening between 4 and 8.

It gives you about the 4. Everything about 8 is in the appendix. It is on page 19. That is for the 4 milligrams, how the events were happening.

DR. NERENSTONE: Are there any other questions?

What I would like to do then is for us to take a break. I would like to be back at 10:45, please.

[Break.]

DR. NERENSTONE: If the sponsor would like to start their presentation on Zometa in the prostate cancer and solid tumors other than prostate cancer and breast cancer.

Sponsor Presentation

Zometa in Prostate Cancer and Solid Tumors Other than Prostate Cancer and Breast Cancer

DR. SMITH: Thank you. I am Matthew Smith. I am an assistant professor of medicine at Harvard Medical School and a medical oncologist at Massachusetts General Hospital. I was a participant in study 039. Good morning.

[Slide.]

My first task is to introduce two double-blind placebo-controlled randomized trials of Zometa in patients with bone metastases, protocol 039 for men with metastatic prostate cancer and protocol 011 for patients with solid tumors other than prostate cancer or breast cancer.

After introducing all studies, I will present the efficacy and safety data for protocol 039. Dr. Robert Coleman will then present the efficacy and safety data for protocol 011.

[Slide.]

The objective of the protocols was to demonstrate that Zometa is superior to placebo for the treatment of bone metastases.

[Slide.]

The primary endpoint for each study was defined as the proportion of patients experiencing any skeletal-related event, or SRE, not including hypercalcemia of malignancy.

[Slide.]

The secondary study endpoints included time to first SRE, skeletal morbidity rate and Andersen-Gill multiple-event analysis. Secondary analyses were also performed considering these outcomes including hypercalcemia of malignancy. Other secondary endpoints include pain and analgesic scores, bone-lesion response, time to progression of disease and safety including survival.

Six months of additional survival in serum-creatinine data were included in the 120-day

safety update.

[Slide.]

SREs were defined as pathological fractures, spinal-cord compression, radiation therapy to treat bone pain or to treat or prevent pathological fractures or spinal-cord compression or surgery to bone. In protocol 039, for men with prostate cancer, the definition of SREs also included change in antineoplastic therapy for bone pain.

Hypercalcemia of malignancy was not included in the definition of SREs for the primary efficacy analyses but was included for some of the secondary analyses.

[Slide.]

These are the preplanned analyses terms. They were defined in the same manner as protocol 010.

[Slide.]

The original study design randomly assigned patients to treatment with Zometa 4 or 8 milligrams or placebo administered as a five-minute infusion. Two renal safety amendments address concerns about renal safety. In June, 1999, renal amendment 1 increased the infusion time from five

to fifteen minutes and increased the volume from 50 to 100 milliliters.

In June, 2000, renal amendment 2 switched the 8-milligram dose to 4 milligrams and all subjects assigned to the 8-milligram dose will be termed the 8/4 group to indicate this change. Renal amendment 2 also introduced monitoring of renal function with measurement of serum creatinine within two weeks before each dose.

Before unblinding of the data, a statistical amendment defined the primary efficacy analysis based on the comparison of the Zometa 4-milligram group versus placebo.

[Slide.]

This figure illustrates the time lines for the renal amendments in patient accrual. In protocol 039, for men with prostate cancer, 368 of 648 men were accrued before renal amendment 1. In protocol 011, for patients with solid tumors other than breast cancer or prostate cancer, 195 of 773 patients were accrued before renal amendment 1.

Both studies completed accrual before renal amendment 2 and treatment and follow up continued through January, 2001. Notably, most patients completed or discontinued the study before

renal amendment 2 and, as a result, as you have already heard, three-quarters of the patients assigned to the Zometa 8/4 group received only the 8-milligram dose.

[Slide.]

Next, I will summarize the design, efficacy and safety data for protocol 039.

[Slide.]

Protocol 039 included men with progressive metastatic prostate cancer. Requirements for study entry included radiographic documentation of bone metastases, rising serum PSA, baseline serum testosterone concentration in the castrate range, no strong opiate analgesics, ECOG performance status of 0, 1 or 2, serum creatinine less than 3 and appropriate neoplastic therapy at study entry.

[Slide.]

Subjects were stratified according to the presence or absence of distant metastases at the time of initial diagnosis with prostate cancer. As in the prior studies, all patients received supplemental vitamin D and calcium and Zometa was administered every three weeks for fifteen months.

[Slide.]

The groups were well balanced in most

baseline demographic and prognostic factors. The mean age was 71 to 72 years. Approximately 10 percent of the men were black. Most men had an ECOG performance status of 0 or 1. Median PSA at study entry was 61 to 89 and both Zometa groups had higher median PSA values than the placebo group.

[Slide.]

Patient dispositions by group are shown here. As expected for this population of older men with metastatic prostate cancer, about one-third of men in each group completed fifteen months of treatment. The Zometa 4-milligram group had the highest rate of study completion.

[Slide.]

This table shows the reasons for early discontinuation. Discontinuation due to an unsatisfactory therapeutic effect was more common in the placebo group than the Zometa groups. Rates of early discontinuation for other reasons were similar for all groups. These data are similar to the historical results of placebo-controlled trials of pamidronate in breast cancer.

[Slide.]

The primary efficacy analysis is shown in this figure. 44 percent of men in the placebo

group experienced one or more SREs by fifteen months. In both Zometa groups, the proportion of men with an SRE was less than the placebo group. The primary efficacy analysis was positive. 33 percent of men in the Zometa 4-milligram group experienced an SRE. This improvement was statistically significant compared to placebo and the p-value for that comparison is 0.021.

Notably, the improvement in the Zometa 4-milligram group remained significant even when fractures were excluded as an SRE. 38 percent of men in the Zometa 8/4 milligram groups experienced and SRE although this improvement compared to placebo did not reach statistical significance. Thus, while the primary efficacy analysis of the Zometa 4-milligram group was positive, the results from the 8/4 group raised two important questions.

[Slide.]

First, why was no dose effect observed? The doses of Zometa, as you have already heard, were chosen based on early dose-finding studies and, as Dr. Robert Coleman has nicely introduced, Zometa targets the osteoclasts. NTX is a biochemical marker of osteoclast function and approximately 70 percent inhibition was achieved in

both Zometa groups, 4 and 8/4, and this inhibition was maintained throughout the duration of the study.

So, with maximum target inhibition in the Zometa 4-milligram group, it is not surprising that no dose effect was observed.

[Slide.]

The second question, how should the results of the Zometa 8/4 milligram group be interpreted relative to the positive primary efficacy analysis in the 4-milligram group? This is a revised slide.

We attempted to address this issue in a combined analysis of both Zometa groups compared to placebo. As you recall, the proportion of men with an SRE in each Zometa group was less than the placebo group. In this combined analysis, SREs were reduced from 44 percent in the placebo-treated group to 36 percent in the combined Zometa groups. This risk reduction was significant compared to placebo. The p-value for this comparison was 0.041.

I would also like to add that the treatment effect observed, even in this combined analysis, compares quite favorably with the

original pivotal placebo-controlled trials of pamidronate in breast cancer.

The efficacy of Zometa across a spectrum of skeletal-related events further supports the effectiveness of Zometa in metastatic prostate cancer.

[Slide.]

This figure shows SREs by type and treatment group. For all groups, the most common types of SREs were radiation to bone and fractures. The risk of these and other events were consistently lower in the Zometa group than in the placebo group.

[Slide.]

Kaplan-Meier estimates of time to first SRE are shown here. The median time to first SRE was 321 days in the placebo group. The median time to first SRE was longer in each of the Zometa groups. After 420 days, the median time to first SRE was not yet reached in the Zometa 4-milligram group and this improvement in time to first SRE is statistically significant. The p-value is 0.011.

[Slide.]

SREs were also analyzed as events per year or skeletal morbidity rate. The SMR was lower in

both Zometa groups than in the placebo group. Compared to placebo, the SMR in the Zometa 4-milligram was decreased by 46 percent. This improvement, again, was significant.

[Slide.]

Andersen-Gill multiple-event analyses were performed to provide a robust evaluation of the changes in event rate over time. Compared to placebo, the hazard ratios for each of the Zometa groups were less than 1. The risk reduction in the Zometa 8/4 group was 15 percent. The risk reduction in the Zometa 4-milligram group was 36 percent and significant compared to placebo.

[Slide.]

This is a new slide. As an exploratory analysis, we also evaluated the proportion of men with an SRE based on the radiographic classification of bone lesions. Bone lesions were classified as lytic, blastic or mixed. For this analysis, men were defined as members of the lytic subset if they had one or more lytic lesion regardless of whether they had many other blastic metastases.

They were classified as the blastic subset if they had exclusively blastic lesions and other

if they could not be defined in either the lytic or blastic subset. For all, the lytic, blastic and other subsets, the Zometa groups had fewer events than the placebo group. This consistent treatment effect can be clearly seen in the blastic and other subsets.

The result in the lytic subset is a bit more varied where you do a more dramatic treatment effect in the 4-milligram group but I would also point out that few patients were in this subset and this is subject to more random variation.

Again, while this subset analysis has limitations, it suggests that Zometa is effective in prostate cancer across the spectrum of radiographic classifications of lesions.

[Slide.]

Here we see disease-related endpoints. The time to progression of bone lesions and time to disease progression were similar for all the groups.

[Slide.]

At study completion, changes in analgesic scores, ECOG performance status and FACT-G total scores were similar for all groups. Pain scores increased from baseline for all groups. The

increases in pain scores were attenuated in both Zometa groups. Compared to the placebo group, the relative improvements in pain scores were significant at all time points for the Zometa 8/4 group and at three and nine months for the Zometa 4-milligram group.

[Slide.]

This table summarizes the efficacy data for Zometa in men with prostate cancer. Compared to placebo, both Zometa groups showed improvements in the proportion of men with any SRE, time to first SRE, mean SMR and multiple-event analysis hazard ratios.

For the Zometa 4-milligram group, the improvements in each of these outcomes were statistically significant. Collectively, the efficacy data showed that Zometa decreases skeletal complications in men with metastatic prostate cancer.

[Slide.]

The safety data for protocol 039 is summarized in the next few slide.

[Slide.]

Causes of death during the trial or within 28 days of drug termination were similar for all

groups. As expected for this patient population, chance of progression was the most common cause of death for all groups.

[Slide.]

There were no statistically significant differences in overall survival between the groups. The median survival in the Zometa 4-milligram group was about three months longer than the placebo group. The p-value for this comparison was 0.087.

[Slide.]

This slide summarizes the common adverse events. Events that occurred at least 5 percent more often than placebo are highlighted in yellow. Events that occurred at least 5 percent less often than placebo are highlighted in green. Adverse events related to intravenous bisphosphonates including pyrexia and myalgias were more common in the Zometa groups. Bone pain was less common in the Zometa 4-milligram group than in the other groups.

[Slide.]

Grade 3 or grade 4 anemia occurred in less than 10 percent of men in all the groups. Grade 3 or 4 anemia was more common in the Zometa 8/4 group than in the other two groups. Blood transfusion

and treatment with erythropoietin were somewhat more common in the Zometa groups than placebo.

Grade 3 or 4 hypocalcemia was observed in less than 2 percent of patients in all groups. Grade 3 or 4 hypermagnesemia and hypophosphatemia were more common in the Zometa groups than placebo although no patient experienced symptoms related to these mineral changes.

[Slide.]

This slide shows NCI grade 3 and 4 serum creatinine changes after renal amendment 1. For men randomized to the study after renal amendment 1, there were no grade 4 changes in serum creatinine in any of the groups. Grade 3 changes in serum creatinine were uncommon but a few more events were observed in the Zometa groups than in the placebo group.

[Slide.]

This slide shows Kaplan-Meier estimates of the first increase in serum creatinine. It follows the same format at Dr. Berenson's talk and serum creatinine increase was defined in the same manner as protocol 011.

Patients randomized prior to renal amendment 1 are shown in the upper panel. Patients

randomized after renal amendment 1 are shown in the lower panel. Before renal amendment 1 the risk of serum creatinine increase was significantly higher in the Zometa groups. Compared to placebo, the hazard ratios for the Zometa 4-milligram group and 8/4 groups were 2.0 and 4.0 respectively.

After renal amendment 1, excess risk of serum creatinine increase was markedly reduced in the Zometa 8/4 group. The excess risk was nearly eliminated in the Zometa 4-milligram group with a hazard ratio of 1.1. These results highlight the success of fifteen-minute infusion time in improving the renal-safety profile.

[Slide.]

The safety data indicate that Zometa is well tolerated. Adverse events associated with bisphosphonates were more common in the Zometa groups than placebo. The renal-safety profile of Zometa 4-milligrams over fifteen minutes is similar to placebo in men with prostate cancer.

[Slide.]

Collectively, the protocol 039 data indicate that Zometa decreases complications in men with prostate cancer and bone metastases.

Thank you for your attention. Dr. Robert

Coleman will now present the efficacy and safety data for protocol 011.

DR. COLEMAN: Good morning again.

[Slide.]

It is my pleasure to present the third of these randomized clinical trials and to focus on the data in protocol 011 which included solid tumors other than prostate cancer or breast cancer in a placebo-controlled trial.

Dr. Matthew Smith has already given you the definitions for the endpoints. He has also highlighted the renal safety changes and how that affected the recruitment times. So I am going to go straight into the trial design which is shown on this slide.

[Slide.]

These patients had to have histological confirmation of advanced malignancy from a tumor other than prostate or breast cancer and had to have radiographic evidence of at least one bone metastasis. On entry into the study, they were allowed to be on appropriate antineoplastic therapy and this therapy could be changed as was appropriate during the study period.

They had to have reasonable renal function

with a serum creatinine below 3 milligrams per deciliter and they had to be of ECOG performance status 0, 1 or 2.

[Slide.]

Prior to randomization, patients were stratified into two groups, either non-small-cell lung cancer or all other solid tumors which included some 20 different primary-tumor types. The most common are shown here, being renal-cell cancer, small-cell lung cancer, carcinomas of unknown primary type, bladder and colorectal.

As for protocol 011 and protocol 039, all patients received supplemental vitamin D and calcium. The dose and dosing regimens were as defined in the protocol 039 study, namely patients received Zometa at 4 or 8, as you have heard subsequently reduced to 4 milligrams, or placebo as a five-minute infusion initially subsequently amended to fifteen minutes. This was given on a three-weekly basis.

Because of the short survival prospects of these patients, the endpoint was chosen to be at nine months after eight infusions.

[Slide.]

The demographics and prognostic factors

for protocol 011 are shown on this slide. The mean age was similar at around 60 in all three treatment groups. About two thirds were male. Some 90 percent were Caucasian with other ethnic groups relatively infrequently represented. Around 80 percent were of apparently good performance status, with a performance status of 0 or 1 on the ECOG scale and had reasonable quality of life with a FACT-G score of around 70 with 100 being performance quality.

You can see that the stratification resulted in about one-half of patients entered into the study having a diagnosis of non-small-cell lung cancer and the other half being the other solid tumors. Because of the stratification, they were well-balanced between the three treatment arms.

[Slide.]

As a reflection of the poor prognosis of these patients, only 25 percent of patients completed study therapy out to nine months which means that three-quarters withdrew from the study therapy due to various reasons which will be shown on a subsequent slide. However, where possible, patients were followed after therapy discontinuation until the nine-month endpoint.

[Slide.]

This slide summarizes those reasons for early discontinuation. The most common cause was death, nearly always due to the underlying malignancy. Next were adverse events. Again, most of these were adverse events associated with that malignancy rather than the treatments being administered. And just under 20 percent withdrew their consent. Again, this was usually due to deteriorating performance status and the difficulties of attending for regular infusion therapies.

The other reasons for withdrawal are relatively uncommon and are listed on this slide and show no differences between the three treatment groups.

[Slide.]

I will now take you to the results and the primary efficacy analysis which you will recall was the proportion of patients experiencing and SRE. Also, on this slide, is the time to first SRE for the three treatment groups.

On the left-hand panel, you see the proportion of patients experiencing one or more events. It was 44 percent in the placebo arm which

was reduced to 38 percent in the Zometa 4 milligrams but with a p-value which did not reach significance of 0.127. For the 8-milligram dose, it was 35 percent which did reach significance with a p-value of 0.023.

However, on the right-hand side is the time-to-first-event analysis which, as we have already heard from Dr. Williams, is the preferred--or the statistician's preferred analysis of these data and takes into account the fact that many patients drop out due to death and other reasons, and that is not well-reflected in the time to first SRE analysis--I'm sorry; in the percent of patients analysis.

In the time to first SRE analysis, it is clear that both treatments are working with an extension in time to first SRE for approximately two to three months and a difference of about 10 percent which appears three months into therapy and persists out to at least eight months, as shown on this graph.

So, in this analysis, both dosages show significant improvements over placebo with p-values of 0.023 and 0.034 for the 4-milligram and the 8-milligram groups respectively.

[Slide.]

As you have seen before, here is a slide showing the individual components which may cut the SREs. There is a reduction for both Zometa groups in terms of radiation therapy to bone, a reduction, although less marked, in fractures and, as you would expect with infrequent events, little change in terms of surgery to bone or spinal-cord compression rates.

[Slide.]

As with the other studies, skeletal morbidity rates were calculated and analyzed. This slide shows that the skeletal morbidity rate for placebo was 2.5 and was reduced to 2.24 in the Zometa 4-milligram arm which did not quite reach significance at 0.069 and was significantly reduced to 1.55 in the 8-milligram treatment arm.

[Slide.]

As for the other protocols, an Andersen-Gill multiple-event analysis was performed. The main reason for this is to look at the possible differences between the strata as well as the differences between the treatment arms.

You can see that the hazard ratio, looking at the 4-milligram data, is very similar for non-small-cell

lung-cancer patients as it is for other solid tumors with approximately 27 percent risk reduction. For the Zometa 8/4 milligrams, overall, there is a 32 percent risk reduction with an apparent increased efficacy in lung cancer than in other solid tumors but the numbers, obviously, are relatively small in this subset analysis.

[Slide.]

This slide, like in the previous presentations, has been added and I am sorry for the people who are not on site who don't have access to this slide, but it shows the breakdown of SREs in terms of the radiographic appearances of their lesions on study entry. So, as before, there is a group of patients with at least one lytic lesion plus-or-minus other types throughout the skeleton. They are labeled as lytic, a group with only blastic disease, labeled as blastic, and a group that fall between those two extremes, labeled other.

The slides shows that in the lytic metastases, there is a reduction in favor of both treatment arms compared to placebo. There is also a reduction in the blastic patients. The group in the middle, the other patients, there is no obvious

change and we would suggest that that is more to do with classification of radiographic subtypes than a biological underlying reason for why that group show no difference from placebo.

[Slide.]

Turning now to disease-related endpoints, time to progression in bone and time to progression of the overall disease is shown here in days. In comparing the 4-milligram arm to placebo, there was no difference in time to progression in bone or overall progression. There is a suggestion with the 8-milligram dose that bone progression is delayed from 109 to 238 days.

[Slide.]

As with the other studies, a number of quality-of-life-related issues were assessed. These included the brief pain inventory score, analgesic scores, ECOG performance status and the FACT-G quality-of-life assessment.

Between the three treatment arms, there were no significant differences in these quality-of-life endpoints. In other words, pain was little changed through the nine-month period. Analgesia increased slightly. There was approximately a 1.0 increase in performance status and a small decline

in quality of life, but no discernible or statistically significant differences between the Zometa arms and placebo.

[Slide.]

So, to summarize the efficacy, as we have seen before, the four different analyses, the proportion with a skeletal-related event, the time to first event, the skeletal-morbidity rate and the Andersen-Gill analysis, the results are positive for all analyses for the 8-milligram dosage and are statistically significant for the time to first SRE in the 4-milligram dosage group.

We would, therefore, conclude that Zometa is the first bisphosphonate to demonstrate efficacy in decreasing skeletal complications in this broad range of solid tumors.

[Slide.]

Finally, the safety analysis from protocol 011.

[Slide.]

This slide shows the primary cause of death during the trial or within 28 days after study-drug termination. The most frequent cause of death was the underlying malignancy followed by respiratory complications which is, perhaps, not

surprising for a population of non-small-cell lung-cancer patients.

The other causes of death were infrequent and are very similar between the treatment groups with renal and urinary causes of death being very unusual.

[Slide.]

Here is the Kaplan-Meier plot for survival. There is no significant difference between any of the three treatment arms with a median survival of just six months.

[Slide.]

Here is a similar slide to the one you have seen before of adverse events occurring in more than 15 percent of patients. There are very few events that are more frequent in the Zometa-treated arms. In particular, in this trial, the acute-phase reactions were unusual and did not appear on this slide. There was a slight reduction in bone pain as an adverse event in the Zometa-treated patients and odd increases in nausea, dyspnea and headache of uncertain reasons in the Zometa 4-milligram treatment arm.

[Slide.]

In terms of hematology, electrolyte and

mineral changes, anemia incidence was low at less than 5 percent for all treatment groups but was slightly higher in the Zometa-treated cohorts. However, the use of red blood cells and erythropoietin was similar for all treatment groups.

Electrolyte and mineral adverse events were uncommon with an instance of hypercalcemia of less than 2 percent for all treatment groups, but there was a higher incidence of hyperphosphatemia in Zometa-treated groups although this was not of any clinical significance and related symptoms were not reported.

[Slide.]

This slide shows the NCI grade 3 and 4 serum-creatinine changes in the patients enrolled after the fifteen minutes of measurement. It shows firstly that grade 3 and 4 changes are rare, at around 1 percent, 1 to 2 percent, and there was no difference in these severe events between the Zometa arms and the placebo arm.

[Slide.]

You have seen this kind of analysis before. It is the Kaplan-Meier estimate of first serum-creatinine increase with the top panel

showing the Kaplan-Meier estimate before the infusion-time amendment and the bottom panel the same sort of plot after the fifteen-minute infusion change.

The top part of the panel shows that both Zometa arms were associated with an increased risk of renal dysfunction with a hazard ratio of 3.8 for Zometa 4 and 2.9 for Zometa 8. After the amendment, there is a substantial reduction in the hazard ratio for both treatment arms although some increased risk persists over and above placebo with the hazard ratio for the 4-milligram arm being 1.6 with a p-value of 0.0228.

[Slide.]

So, to summarize the safety, adverse events commonly associated with bisphosphonates such as hyperphosphatemia and anemia were reported more frequently in the Zometa-treated groups. The risk of renal deterioration was moderately higher in the Zometa 4-milligram treatment group even at the fifteen-minute infusion than it was in the placebo group.

[Slide.]

I would, therefore, conclude, in overall summary, that Zometa is the first bisphosphonate to

demonstrate efficacy in decreasing skeletal complications across this broad range of solid tumors affecting bone and that Zometa, when given at a dose of 4 milligrams over fifteen minutes has an acceptable safety profile which is probably very similar to the safety profile of intravenous pamidronate, 90 milligrams.

Thank you very much for your attention. I will now pass over the podium to the next speaker, Dr. David Parkinson.

Conclusions

DR. PARKINSON: Thank you, Rod. I am David Parkinson from Novartis Clinical Research.

[Slide.]

Before I summarize and conclude the Novartis part of the presentation today, we wanted to take this opportunity to thank the hundreds of investigators and research staff at literally hundreds of sites in thirty countries around the world. We also wanted to express our appreciation to the more than 3000 patients who have contributed to these studies.

[Slide.]

We believe that the problems which are being addressed here today are, in fact, extremely

important to cancer patients. As you have heard from Dr. Coleman earlier, the consequences of bone metastases are very serious events in the lives of cancer patients. Current therapy is clearly inadequate to meet to clinical needs of this broad population.

The reason we began this very large and complex clinical program is that we had significant preclinical data suggesting the superior potency of Zometa in inhibiting osteoclast activity when one compared that activity with the entire range of other bisphosphonates, pamidronate included.

The current treatment program, therefore, was designed to test the efficacy of Zometa across a broad range of tumors beyond the areas where we knew the pamidronate was effective.

[Slide.]

We have presented here, this morning, data from three large international controlled double-blind and, in the case of protocol 010, double-dummy randomized clinical trials. As I have indicated, these trials have included more than 3000 patients with breast cancer, myeloma, prostate cancer and the range of other solid tumors.

To reemphasize what you have heard, this

is the largest clinical-trial program ever conducted to evaluate the efficacy and safety of bisphosphonates in patients with cancer metastatic to bone.

[Slide.]

Our initial experience with this agent showed that, with higher doses and/or with shorter infusion times, renal events occurred which were characteristic of those associated with all other intravenous bisphosphonates. But we believe we have shown you that, by increasing the infusion time to fifteen minutes and by using the 4-milligram dose of Zometa, the renal-safety profile does not differ from that of pamidronate.

Furthermore, the safety profile is consistent for other adverse events, other toxicities, with that similarly typically seen with other intravenous bisphosphonates.

[Slide.]

With respect to efficacy, going across the range of tumors, we believe that we have shown that the effectiveness of Zometa as compared to pamidronate has been reliably established in preplanned analyses, as you have heard, of the range of the skeletal-related events with this

noninferiority design that we have talked so much about.

[Slide.]

Furthermore, in the range of solid tumors, we believe that there is consistent benefit across the range of skeletal-related-event analysis with a relative reduction of 14 percent in the proportion of patients having skeletal-related events. Importantly, we see an extension of the median time to this first event by more than two months. That represents a 27 percent reduction in relative risk in a very poor-prognosis patient population, as you have just seen.

This is the first clinical trial demonstration of bisphosphonate benefit in these patient populations.

[Slide.]

Prostate cancer, protocol 039, we believe represents a clear demonstration of efficacy, both in terms of the 25 percent relative reduction of SREs as well as with the extension of the time to first SRE by, in this case, more than 100 days representing a 33 percent relative risk reduction as compared to placebo.

Again, this is the first demonstration of

such benefit in patients with prostate cancer and an important addition, we submit, to the therapy of prostate-cancer patients.

[Slide.]

To conclude, we have confirmed the activity, we believe, of Zometa in breast cancer and myeloma. We have demonstrated extension of that clinical benefit to the range of other tumors. We believe that the consistency of this efficacy is an important characteristic of the drug, that it extends across all three trials, across multiple tumor types and with multiple endpoints.

Furthermore, the efficacy is observed in patients with bone lesions ranging from osteolytic to osteoblastic in radiological appearance. Importantly, this efficacy is observed with a safety profile similar to that to pamidronate and with a much more convenient administration time.

We thank you for your attention this afternoon--still this morning--and look forward to further discussions.

Thank you.

DR. NERENSTONE: Thank you. We will now go on to the FDA presentation.

FDA Presentation

Zometa in Prostate Cancer and Solid Tumors
Other than Prostate Cancer and Breast Cancer
(Studies 010, 011 and 039)

DR. IBRAHIM: Good morning. I am Amna Ibrahim and I will be discussing the issues related to the efficacy of two trials. The first trial to be discussed with be in prostate-cancer patients. This will be followed by a discussion of the solid-tumor trial.

[Slide.]

This is the first indication for a bisphosphonate for prostate-cancer patients. As already pointed out by Dr. Williams, the main issue for the prostate-cancer study is the lack of concordance in the 4- and 8-milligram arms of the prostate-cancer trial.

The critical questions for the study are considering both the 4-milligram and the 8-milligram arms, how convincing is the prostate-cancer trial. Can the data from other studies provide support?

[Slide.]

The overview of my presentation on efficacy of the prostate-cancer study will be as follows. We will go through the study results and

some of the exploratory analysis. Then there can be several reasons to explain the lack of concordance in the two Zometa arms such as baseline imbalances and large numbers of early discontinuations.

I will represent to you the division's conclusions regarding the possibility of baseline imbalances. No impact of early discontinuations could be found on the result of the primary endpoint. At the end, a summary of the issues will be presented.

[Slide.]

This slide illustrates the protocol-specified primary endpoint; that is, proportion of patients with at least one SRE. The second column from the left shows the proportion of patients with at least one SRE. The third and fourth columns give the p-value and confidence intervals.

33 percent of patients in the 4-milligram arm had at least one SRE. This was statistically better than placebo with a p-value of 0.021. 38 percent and 44 percent of the patients in the 8-milligram and placebo arm, respectively, had at least one SRE. These were not statistically different from each other. The p-value was 0.222.

[Slide.]

We had similar results for time to first event. The 4-milligram arm is better than placebo statistically with a p-value of 0.009 whereas the 8-milligram arm is no different statistically from placebo with a p-value of 0.541. The median time to first event was not reached for the 4-milligram arm. There was a trend towards improvement for 8 milligrams. This is lack of concordance between the results of the two Zometa arms. The lower dose of the 4-milligram arm appears to be effective where as the higher dose of 8-milligram arm does not demonstrate efficacy.

[Slide.]

This slide shows hazard ratios of the comparison of each Zometa arm versus placebo in the two studies I am presenting. Study 011, in red, illustrates the hazard ratio in the solid-tumor trial the discussion of which will follow the prostate-cancer trial. Then, in green, you can see the hazard ratios for the prostate-cancer trial, that is trial 039.

The point estimates for the hazard ratios and the 95 percent confidence interval were less than 1 for the 4-milligram arm. The point estimate

for 8 milligrams was 0.912. The upper end of the 95 percent confidence interval of hazard ratio was over 1 at 1.226.

[Slide.]

The secondary endpoints shown here showed no statistical difference across the three arms of the study.

[Slide.]

The next three slides present to you analyses that were not prespecified and are exploratory in nature.

[Slide.]

When the results of the two Zometa arms are pooled together, the p-value for time to first SRE was borderline at 0.06. The point estimate of the hazard ratio was 0.781 with the upper end of the 95 percent confidence interval as 1.01. Looking at the proportion of patients with any first event, the p-value was 0.04. The point estimate for the difference of proportions was -0.08.

[Slide.]

Individual SREs may be evaluated in several ways with pros and cons existing for each method. This graph has been reproduced from the

sponsor's briefing package. It represents the proportion of patients with the individual types of SRE. This was not the prespecified analysis.

Each type of SRE such as radiation fracture or any other SRE was counted the first time it occurred in that patient regardless of the number of times it occurred subsequently. In this method, an event of a pathological fracture which resulted in surgery and radiation would show up in three different categories.

[Slide.]

Can we rely on evidence from other trials in the NDA for blastic metastases? Can we draw support from the results of the breast-cancer and myeloma study or from the other solid-tumor study? This graph presents the findings in a subgroup of patients in the solid-tumor trial. It gives the proportion of patients with any SRE in patients in whom metastasis was blastic at baseline.

There were a total of 133 patients in the solid-tumor study with blastic only met at baseline. 42 of them were in the 4-milligram arm, 51 in the 8-milligram arm and 40 in the placebo arm. Eleven and fifteen patients in the 4-milligram and 8-milligram arms and 14 patients in

the placebo had any SREs. No conclusions can be drawn regarding effect of Zometa from the solid-tumor study due to the subgroup analysis and the relatively small number of patients.

Does literature provide support for the efficacy of a bisphosphonate in prostate cancer? There were no large randomized trials published for the effect of bisphosphonate in prostate cancer for SREs.

Does any other study provide support of a bisphosphonate in prostate cancer? Novartis showed a slide on the effect of Aredia on proportions of patients with SREs in Aredia and placebo. Their conclusion was that no effect was demonstrated. This data has not been submitted to FDA for analysis.

[Slide.]

We did not detect any baseline imbalances in the three arms. Prior SREs, baseline PSAs and the analgesic scores were important prognostic factors for both arms. In the multivariate Cox regression model, however, these factors did not alter the overall time to first SRE results. The 4-milligram arm remained significantly better than placebo. The 8-milligram arm was, again, not

statistical different from placebo.

[Slide.]

Early discontinuations were not the reason for the discordant results of the two treatment arms. Early dropouts ranged from 62 to 72 percent in the three arms by the end of the fifteen months. The number of infusions administered were similar at three months implying an equal number of patients treated. However, the number of SREs were already diverging by three months.

[Slide.]

Both proportions of patients with SRE and time to first SRE for the 4-milligram arm were significantly better than placebo. There was no difference statistically for both these endpoints between the 8-milligram arm and placebo.

[Slide.]

As you have heard, the 8-milligram arm was dropped from the trial due to safety reasons. It may be argued that the 8-milligram arm should be ignored completely. This guidance states that, when considering a single multicenter trial, all available data should be examined to either support or undercut reliance on a single multicenter trial.

[Slide.]

Another guidance states that support may be drawn from another trial if the other trial was conducted in a disease considered to be biologically similar to the trial in question. Since this is a first indication for an osteoblastic tumor, we will be interested in your opinion to this question; are osteoblastic lesions biologically similar to osteolytic lesions.

[Slide.]

I will conclude the presentation on the prostate-cancer trial by the summary of issues. Considering both the 4-milligram and 8-milligram arms, how convincing is study 039? This is the first indication of a bisphosphonate for a predominantly osteoblastic disease. Can support be drawn from other trials? Is there substantial evidence to support efficacy of the 4-milligram arm?

[Slide.]

The next discussion will be on the solid-tumor trial.

[Slide.]

As with the previous presentation, primary endpoint results will be presented. This will be followed by issues raised because of the

heterogeneity of the patient population. SREs may be affected by the concurrent therapy and issues dealing with chemotherapy will be presented. At the end, the summary of issues of this trial will be discussed.

[Slide.]

38 percent of patients in the 4-milligram arm of Zometa had at least one SRE which was statistical no different to the 44 percent of patients in the placebo arm. The 8-milligram arm showed a statistical improvement over placebo. The 4-milligram arm, in this study, did not prove statistically significant superiority over placebo in the protocol-specified primary endpoint.

[Slide.]

This slide presents the FDA preferred endpoint of time to first SRE. In these patients, the was a 67-day improvement over placebo in time to first SRE in the 4-milligram arm of Zometa. It should be noted that this improvement occurred in a group of patients who had a median survival of less than seven months.

[Slide.]

This slide shows an exploratory analysis where the results of both Zometa arms were pooled

together. The p-value for time to first event was 0.01. The hazard ratios were less than 1 for point estimate as well as 95 percent confidence interval. The p-value for the proportions of patients with any SRE was 0.03.

[Slide.]

The population included in this trial is heterogeneous. Different tumor types have a varying predilection for the metastases to bone. The different tumor types may have a variable behavior in the bone. Lastly, there may be a potentially variable response to Zometa in the diverse tumor types in the study.

[Slide.]

This slide is meant to show the tumor types included in the study. They were fairly evenly balanced except for the renal-cell-cancer patients that was slightly more in the 4-milligram arm.

[Slide.]

SREs may be affected by response to chemotherapy. Prior chemotherapy treatment was not recorded. However, the study was blinded and randomized and it is likely that it does not impact on the study results.

[Slide.]

Summarizing the other solid-tumor trial, there was no statistical difference for the 4-milligram arm for the protocol-specified endpoint. There was substantial evidence for the 4-milligram arm for time to first SRE and there was substantial efficacy for the 8-milligram arm in both endpoints; that is, proportion of patients with any SRE and for time to first event.

[Slide.]

Issues of the other solid-tumor trial. There was a heterogenous population. Is there substantial evidence to support efficacy of the 4-milligram arm? If yes, should Zometa be approved for all solid tumors?

Thank you. Dr. Nancy Scher will now present to you the safety data.

Safety Data

(Studies 010, 011 and 039)

DR. SCHER: Good morning.

[Slide.]

I am Dr. Nancy Scher and I will discuss the safety analysis of the three trials.

[Slide.]

Early in the course of the bone-metastases

trials, renal safety became a concern when three patients were reported with acute renal failure. The protocol was amended to improve safety. The infusion time was increased from five to fifteen minutes. The Zometa 8-milligram dose was decreased to 4 milligrams and, as you heard, this became the 8/4 milligram arm of each study.

Serum-creatinine monitoring was required before each dose. Zometa was to be held for renal deterioration as previously defined and resumed when the creatinine was within 10 percent of baseline.

[Slide.]

This table shows renal deterioration by baseline creatinine for the breast and myeloma patients who were randomized after fifteen-minute infusion amendment. The first row shows the number of percentage of patients with normal baseline creatinine who developed renal deterioration according to treatment arm. The second row shows patients with abnormal baseline creatinine. The third row shows the outcome for all patients.

The percent renal deterioration was similar for Zometa 4-milligram and Aredia. Renal deterioration occurred in patients with normal and

with abnormal baseline creatinine. The renal effects seem dose-dependent for Zometa 8 arm compared to the 4-milligram arm.

[Slide.]

For this Aredia-controlled study of patients with multiple myeloma and breast cancer, the incidence of adverse events was similar for Zometa and Aredia. Slightly more patients in both Zometa arms had a greater than 25 percent from baseline decrease in hemoglobin. The incidence of renal-function deterioration was greater for Zometa 4 than for Aredia prior to the fifteen-minute infusion amendment, as you have heard.

Post-amendment, the incidence was similar for Zometa 4 and Aredia. The time to first renal deterioration was similar by Kaplan Meier analysis.

[Slide.]

This table shows renal deterioration by baseline creatinine for prostate-cancer patients who were randomized following the fifteen-minute infusion amendment. The incidence of renal deterioration was slightly higher for Zometa 4 than placebo. For the entire group and for patients with normal creatinine, rows 1 and 3, the effect was greater with Zometa 8.

Perhaps the small number of patients with abnormal baseline creatinine in the Zometa 4 group exaggerates the adverse effect in this arm compared with placebo and even compared with Zometa 8.

[Slide.]

This table shows renal deterioration by baseline creatinine for patients with solid tumors excluding prostate and breast cancer who were randomized following the fifteen-minute infusion amendment. The incidence of renal deterioration was greater for Zometa 4 than placebo, both for patients with normal and abnormal renal function.

In this study, the effect was similar for the 4- and 8-milligram treatment arms.

[Slide.]

For the two placebo-controlled studies, adverse events previously reported to be associated with bisphosphonates such as fever, arthralgias, electrolyte and mineral abnormalities were more common with Zometa than placebo, as was anemia. As you heard, there was no increase in grade 3 or 4 hematologic events. The incidence of renal-function deterioration was greater for Zometa 4 than for placebo. This incidence tended to increase over time with duration of therapy.

[Slide.]

Our overall conclusions are that Zometa 4-milligrams when given intravenously over fifteen minutes every three or four weeks has an acceptable safety profile. It is more toxic than placebo but comparable in safety profile to Aredia.

Renal events occurred in patients with normal and abnormal renal function. Particular caution is indicated for patients with abnormal renal function. Patients with creatinine greater than 3 were excluded from the current trials. Zometa is excreted unchanged by the kidneys resulting in an effectively higher exposure for patients with renal dysfunction. Serum creatinine monitoring is appropriate in patients with normal as well as abnormal renal function.

I would like to thank you for your attention. We will be available at the table for questions of clarification now and we will be present for the discussion after lunch.

DR. NERENSTONE: Thank you very much. I will open it up to questions for the committee. I want to remind everyone that we are going to have time afterwards for discussion of the issues. Right now, I really wanted it to be specifically

questions and clarifications.

Questions from the Committee

DR. NERENSTONE: I would like to start by asking Dr. Scher, when you say that you recommend monitored serum creatinine in all patients, how often do you think that that is necessary; before every treatment, every two or three treatments?

DR. SCHER: I feel that the conservative answer would be to model the conduct of the trials after the renal amendments. So that would be to monitor the creatinine prior to each dose.

DR. NERENSTONE: Other questions? Dr. George?

DR. GEORGE: I have a question about the intent-to-treat analysis or approach taken. There were, in both of these studies, a large number of discontinuations prior to the scheduled end of the study. There was one brief mention that an attempt was made to follow these patients for the primary endpoints. Is there evidence on that point? How many of these that were discontinued, in fact, were followed through the period and how many were just--did that discontinuation mean that no further observation was possible?

DR. SEAMAN: As in any oncology trial,

there were a lot of dropouts, as you said, as you might expect. We have taken into consideration and have done analysis in terms of the three trials to take into consideration whether they dropped out from death or dropped out otherwise. I will gladly show you that information.

Let's take a look at 080.

[Slide.]

If you take into consideration--let's take a look at protocol 011 first and you take into consideration both death and dropouts and look at the time to the first skeletal-related event, you can see the median time still reaches significance for the Zometa 4-milligram group versus placebo with the median time around 127 days for the Zometa 4 group and 85 for placebo.

Can I have the next slide, please, 081.

[Slide.]

Let's look at protocol 010 with the same sort of scrutiny in terms of taking deaths and dropouts. You can see, again, the median time to the first SRE is around 312 days for Zometa 4-milligram and 252 days for the pamidronate 90 milligram. The p-value here is 0.099.

[Slide.]

Finally, for protocol 039, which is the next slide, protocol 042, you can see here, again, taking dropouts and deaths into consideration and looking at the time to the first SRE, we still maintain the significance of 4-milligram treatment group over placebo with the median time being around 337 days for the Zometa 4-milligram group and placebo, 221.

Grant?

DR. WILLIAMS: This occurred to me, too, and I know I asked for an analysis from Novartis and they supplied one about how many--you were supposed to monitor events after going off the drug but it wasn't clear how many of those events actually happened. It was really relatively few. So if I were to redesign the study, I would probably not try to do that because it was a very sketchy collection of data thereafter, I think.

But looking with and without, it didn't seem to make a difference. There were so few events that were collected after going off drug that it didn't seem to make a difference whether you included or excluded them.

DR. NERENSTONE: Dr. George, was your question answered?

DR. GEORGE: Not completely. Let me just state it. We will come back to in the discussion because this is an important issue with respect to what these estimates are of percentage of patients with these events. But, just to be clear, what you showed me there was you assumed any dropout was the same as an SRE at that time.

What I was really asking about was, among those dropouts, and I think, Grant, maybe had answered it, it was very rare after a dropout to actually be able to observe what happened between then and the end of the study.

DR. SEAMAN: That is correct, because of the patient population.

DR. NERENSTONE: Dr. Przepiorka?

DR. PRZEPIORKA: Can you clarify, please, for patients who did develop an SRE, did they stay on study drug?

DR. SEAMAN: Yes; they did. They stayed on study drug and we continued to follow them and they continued to be treated.

DR. PRZEPIORKA: Was there any difference in second, third, fourth or multiple SREs between the treatment arms?

DR. SEAMAN: That was the Andersen-Gill

multiple-event analysis. Basically, you could see from protocols 011 and 039, they were positive.

DR. PRZEPIORKA: Has anyone looked at a hazard plot? We have looked at the rate per year, but patients were restaged at multiple times during the year and the Kaplan-Meier plots seem to drop at three months and a little at six and more at nine months. I was just wondering if there was any point where the hazard for SREs actually plateaued out for all three lines and you have lost the effect of the drug.

DR. SEAMAN: No. I am looking at my biostatistician. We didn't do a hazard plot like that.

DR. PRZEPIORKA: Do you know how long bisphosphonates stay in the bone?

DR. SEAMAN: Yes. From preclinical animal models, they stay in the bone for at least a year after they had received one dose. But that doesn't mean they are pharmacologically active. What happens is the bone is remodeled. It is covered over and an osteoclast buries in exactly that same site where the bisphosphonate is present. It is not reactivated.

DR. NERENSTONE: Mr. Kazmierczak?

MR. KAZMIERCZAK: Gene Kazmierczak. I am a prostate-cancer patient. Both the sponsor and the FDA seem to agree that, when you consider time to the first SRE, that the results in study 011, in both arms of the study, the 4 and 8/4, show a significant improvement from the standpoint of time to the first SRE.

When you look at 039, the 4-milligram arm doesn't show any significance with regard to improvement in time--or does; pardon me--but the 8 doesn't. You did do an analysis that lumped the 4 and the 8 together with regard to numbers of SREs but you didn't do that for time to the first SRE. I noticed by your chart that, when you look at time to the first SRE in the 8/4 arm, it wasn't significant.

Maybe you could explain why.

DR. SEAMAN: I think the FDA medical reviewer did do an analysis of the time to the first SRE and maybe she can answer that. I think it is significant but let her explain.

DR. SRIDHARA: It is barely significant at 0.06. But, you know, this is exploratory and how we interpret this p-value is questionable. We are doing multiple analyses and we are not adjusting

for all of this multiple testing. So it is not correct to be comparing it to 0.05 and say that this is borderline or any of those. It was just an exploratory analysis.

The other thing is, your question, if I understand correctly, we saw that there was no difference in 8 milligrams versus placebo but how come, when we combine together, we saw some difference. That is simply a matter of power and you are putting the two together and, therefore, even a smaller difference you can detect by doing a larger study.

DR. NERENSTONE: Dr. Pelusi.

DR. PELUSI: When Dr. Smith was talking, I just needed some clarification in terms of inclusion into the prostate study. You had on your slide, on page 5, that individuals who were not on strong opioids could be included. I guess I have a few questions about that since many of our patients would be using strong opioids and why the decision was made to--what the definition is of a strong opiate--why the decision was made not to include them and if, in the course of their disease, they required them, did they go off study or were they allowed to take strong opioids?

DR. SMITH: So the definition of a strong opioid was anything stronger than codeine. So that part is easy. Why they were excluded if they needed more pain medicines, that was simply an attempt to define an homogenous patient population. There can be, certainly, variability. That was the basis for doing so.

Patients were not removed from the study if they subsequently required narcotics. As you can imagine, many of these men did.

DR. NERENSTONE: Dr. Bonomi?

DR. BONOMI: Did you collect serial PSA levels in the prostate study?

DR. SEAMAN: Yes; we did. Would you like to see them? Could we have that?

[Slide.]

These are the median PSA levels for the 4, 8/4 and placebo treatment groups over the time course of the study, over the fifteen-month time course of the study. As you can see, they start at the baseline like you saw in the '80s or '60s and, as they progressed, so did their PSA values. We also looked to see was it preceded in terms of were their PSA values elevated prior to their overall progression and the answer is yes.

DR. BONOMI: One other follow-up on that. The baselines are different, too. Are those differences significant?

DR. SEAMAN: We did go and take a look at that information to see if it had an impact on whether or not they were having more progressive disease in terms of their bone disease, and that was not significant when we looked at that.

DR. NERENSTONE: Dr. Lippman?

DR. LIPPMAN: I think that the question Mr. Kazmierczak was getting at and maybe we can discuss this more later, is do you have any suggestions why, in terms of biologic plausibility or statistical, why the higher dose would be less effective than the 4, why the 8/4 was not significant and the 4 was.

DR. NERENSTONE: I think I am going to take the chair's prerogative and say that we are going to leave that for discussion and stick to the questions of specific--for clarification for the FDA and the sponsor because I think that will come up in the discussion. I think it is going to be a question.

Dr. Loehrer?

DR. LOEHRER: Actually, in September last

year, there was a New England Journal of Medicine article that looked at pamidronate in patients with prostate cancer increasing bone-mineral density. I guess I would challenge you, and maybe the inquiring minds that Derek had, in the prostate-cancer population, the challenge was does Zometa work in terms of blastic metastases.

In reality, is it actually a population of patients with osteoporosis. So, putting it, framed in that way, particularly in the patients with prostate cancer, there was no control or at least could you give me the analysis of the time on hormonal therapy prior to going on study and the analysis from that. Similarly, I guess we can go back to the myeloma patients in terms of corticosteroid use and the duration of corticosteroid use prior to going on study.

Or, thirdly, was there a subgroup of patients that had bone-mineral density done that would show us that there weren't any imbalances in any of the arms here?

DR. SEAMAN: I am going to turn this over to Dr. Matthew Smith who actually wrote the paper in NEJM.

DR. SMITH: Thank you for the question.

It can be answered in several ways. First, the time from diagnosis to study entry was similar across all the groups. I will see if we can pull up the data on prior hormonal therapy. I am not sure of that, but if we have it, we will certainly present it to you.

Bone-mineral density cannot be reliably measured in men with metastatic prostate cancer, period. So the bone-mineral-density measurements would be unreliable in this setting.

The question you raise though is have we done something useful in addition to preventing osteoporosis or have we done more than that and prevented disease-related complications, as I understand your question. So the way I asked this question to be looked at and I presented in my talk, but it was a bullet point, was if you look at the primary efficacy analysis for the 4 group and you take out all the fractures, the comparison with placebo remains significant. So I think this is the best way to address the issue of have you done more than treat osteoporosis.

I think that analysis says you have. If you look, also, at the other analysis, looking at the type of events that you prevent, you prevent

radiation therapy to bone. You prevent other kinds of problems that are separate from osteoporosis.

DR. LOEHRER: Could you, again, assure me, then? I am looking for imbalances between the groups and duration of hormonal therapy which we know can predict for more problems with osteoporosis. So what were the differences between the groups with respect to duration of hormonal therapy prior to going on study?

DR. SMITH: John, do we have that data?

DR. SEAMAN: No; we don't. Unfortunately, we don't have the data.

DR. SMITH: I can tell you that the time from diagnosis was similar. We don't have the data for duration of prior hormonal therapy. But I think, again, looking at the clinical endpoint, fractures, if you take them out, the primary efficacy analysis for the 4 group remains significant compared to placebo.

DR. LOEHRER: Just to clarify. Can you get fractures from osteoporosis?

DR. SMITH: That is the concern, that osteoporosis leads to fractures. Osteoporosis is typically defined by a bone-mineral-density criteria. But the reason we are concerned about

that is that it increases the risk of fractures. So, if you take the clinical outcome due to osteoporosis out of the equation, you still have benefit in the Zometa 4 group in the primary efficacy analysis.

DR. NERENSTONE: Dr. Kelsen, Dr. Albain or Dr. Taylor, any questions for the sponsor or for the FDA?

Hearing none, Dr. Brawley?

DR. BRAWLEY: With Dr. Smith there, can we have the last slide that was shown, the one with the PSAs?

[Slide.]

I just want to clarify. The PSA rise over time for the 8/4 group whereas it was relatively stable for the placebo and 4 group. Am I reading that correctly?

DR. SMITH: I will ask for a clarification on how the analyses were done but you have to realize that, as you got out further, you don't have repeated measurements. So the further you go out on this line, the fewer measurements you have maintained. Remember, only about a third of the patients completed treatment at fifteen months. So, once you get out--the second half of this

panel, there is not a lot of time measurement.

So I would interpret the large separation that you see in the right-hand side of this figure very cautiously.

Does that answer your question, Dr. Brawley?

DR. BRAWLEY: Yes. I think it is about the best answer I am going to get right now.

DR. NERENSTONE: Dr. Raghavan?

DR. RAGHAVAN: Matt, coming back to the point that I think Pat Loeher was trying to get at, one of the issues that I think we do need to try to get a handle on is the level of selection of the patient population. When you look at the patients with prostate cancer, the mean or median weights were around 82 kilograms. These are, by and large, relatively chubby patients with prostate cancer.

The length of time from presentation to hitting the study is relatively long. I think it is perfectly sound to have a homogenous population so that is not the question. I think you have achieved that. But my question is do you have a concern that you have subselected out the best patients so that you are not answering the question in the context of killing bad, aggressive prostate

cancer.

These look like pretty good actors. I just wondered, does this tell us something about the group of patients where this may have a role to play?

DR. SMITH: That is a great question. I want to make a couple of comments. First, their survival would argue against being great actors. The medical survival was about one year. It is pretty bad. It is actually worse than most published phase II studies of chemotherapy for hormone-refractory disease.

The second issue of weight I think probably reflects the fact that many of these men have been on hormone therapy for a long time, so you lose lean body mass but you gain fat mass and increase weight. So I think their apparent weights overrepresented their vigor.

DR. NERENSTONE: Dr. Raghavan, go ahead.

DR. RAGHAVAN: Just a point of clarification. Isn't it true, though, that you have got heterogeneity of chemotherapy patients. I think if I read the entry criteria correctly, you have people who are and who are not on chemotherapy. So that would argue against what you

just said for duration.

DR. SMITH: Let me clarify that. Prior chemotherapy was excluded. So, if you had prior chemotherapy, you were excluded. You could go onto chemotherapy during the course of the trial but if you had been on chemotherapy, you couldn't, then, enter the trial.

DR. NERENSTONE: Any further questions from the committee? Dr. Albain?

DR. ALBAIN: I have a question and also Dr. Kelsen did. There was something wrong with our audio feed. It has now been corrected. My question has to do with the pathophysiology of bone metastases and non-small-cell lung cancer in particular and wondering if there is any data that would indicate that the dose response for the bisphosphonate might differ than in the hormone-dependent malignancies of breast or prostate, getting at this issue in the other solid tumors and in lung, in particular, the higher dose seemed to better.

So is there anything in the pathophysiology of the process?

DR. SEAMAN: I will bring Dr. Robert Coleman up to talk to that.

DR. COLEMAN: Robert Coleman. I am not aware of any specific data that have looked at marker changes in lung-cancer patients and compared them to prostate-cancer patients, so it is a good question but I am not aware of any data in the literature to answer it and I don't think we have an analysis of marker changes by disease type. We have marker changes cut in other ways, but not by disease type.

So I am sorry, I don't think I can answer your question.

DR. ALBAIN: Hopefully, we can get that data down the road. To follow up regarding the lung patients, is there any further analysis of use of systemic chemotherapy in this group? We saw a bullet go by that probably there were no imbalances due to the randomization, but how many of these patients were not being treated with systemic chemotherapy versus were? Do you have that data?

DR. SEAMAN: We are looking it up right now. I think we do have that data. Just a second. We have the one prior to. How about, do we have the one after?

[Slide.]

These are the types of chemotherapy. I

don't think you can see these so I will read them to you. The vast majority of patients were receiving chemotherapy, around 75 percent, carboplatin being the number-one agent, paclitaxel second, gemcitabine and cisplatin followed by that. So they were receiving, in 75 percent of the cases, some sort of chemotherapy for solid tumors.

You need to know about non-small-cell lung cancer also; correct?

DR. ALBAIN: Correct. If you have it.

DR. SEAMAN: That was for everything. I'm sorry. I will take that back. If we could go back to the previous slide. That was for all patients. That includes not only non-small-cell lung cancer but it also includes all the other cell and tumors during the course of the trial. I don't think we have it broken down specifically for non-small-cell lung cancer.

DR. ALBAIN: Do you have it by subsequent change in regimen like you did for the other studies?

DR. SEAMAN: Yes; I do. Slide 17.

[Slide.]

In the non-small-cell lung cancer, we broke it down by strata in this. About 16 to 20

percent of the patients stayed on their original regimen. Between 30 and 40 percent of the patients, up to 50 percent of the patients, changed at least one time up to twice for the non-small-cell lung cancer.

In other solid tumors, it is about 30 percent of the patients stayed on their original regimen and then 40 percent changed once and around 12 to 20 percent of the patients changed at least twice.

DR. ALBAIN: Could the camera be moved so I could see the placebo column, please?

DR. SEAMAN: Yes.

DR. ALBAIN: Thank you.

DR. NERENSTONE: Kathy, your question was answered?

DR. ALBAIN: Yes. I just couldn't read the placebo column. It was off-screen. I can see it now. Thank you.

DR. NERENSTONE: Dr. Kelsen?

DR. KELSEN: Thank you. This may have been answered. I may have missed it when some of the audio was lost, but, in trying to get a better understanding as to why, in study 039, there was benefit to the lower dose of Zometa but not as

apparent benefit to the higher dose.

In the briefing book, it indicates that Aredia was also studied in prostate cancer and failed to show benefit. Could you give us any data? Was there a similar trend toward benefit that didn't reach statistical significance? Was there a complete absence of benefit? Was there any reason to suspect that osteoblastic lesions really are more resistant to bisphosphonate therapy?

DR. SEAMAN: In the study that was conducted in the prostate-cancer trial with pamidronate, when we looked at the data from there, we could not detect a benefit in skeletal-related episodes. However, that was not the primary-efficacy endpoint in this trial. The primary efficacy endpoint was sized for pain.

It may be a reflection of the design of the trial in terms of the inclusion criteria, but we certainly did not see a benefit from the 90 milligram treatment group compared to placebo in that trial.

DR. KELSEN: Thank you.

DR. NERENSTONE: Any other questions from the committee? Dr. Przepiorka?

DR. PRZEPIORKA: Just to clarify about the

quality-of-life indicators, please. If you could just summarize--if what I am summarizing, let me say, it is true that there is no difference in the quality-of-life indicator, or the change in quality-of-life indicators, between the 4-milligram arm and placebo for the prostate-cancer trial and the solid-tumor trial?

DR. SEAMAN: That's correct.

DR. PRZEPIORKA: There is no difference in three of the four indicators for the breast cancer myeloma trial and, actually, the Aredia arm fared better in some of the subscales for the FACT-G trial?

DR. SEAMAN: That's correct. But you should make sure you look at that FACT-G scale with some concern because that change, when you look at the literature, is probably not clinically relevant in terms of the numbers you are seeing there. It also should be remembered that we would not expect to see a difference between the three active controls in this sort of study in protocol 010.

DR. NERENSTONE: Dr. Ibrahim?

DR. IBRAHIM: Just a clarification for study 011. It will be difficult to look at any one individual strata. It would be difficult because

there were small-cell patients in the non-small-cell stratum. There were several small-cell patients, small-cell lung-cancer patients, who were there. So it will be difficult to--an intent-to-treat analysis will be different from the actual fact. It could be.

DR. NERENSTONE: Thank you.

Right now, it is 12:15, for those of us in Washington. We are going to break for forty-five minutes and return at 1 o'clock. So, our people at remote areas, it will be a forty-five minute break.

Thank you.

[Whereupon, at 12:15 p.m., the proceedings were recessed, to reconvene at 1:00 p.m., this same day.]

A F T E R N O O N P R O C E E D I N G S

[1:00 p.m.]

DR. NERENSTONE: Dr. Williams, if you would like to start us off.

Introduction to the Issues

DR. WILLIAMS: To begin this afternoon's session, I will briefly introduce the questions that we have prepared. You should have a copy of the questions in your packet. You will probably want to refer to them.

On the first page, you will find two tables that summarize the Zometa efficacy findings. These will be useful as a reference as we proceed.

The first table summarizes the noninferiority study of Zometa versus Aredia in breast cancer and myeloma. The second table summarizes the two placebo-controlled studies, one in prostate cancer and the other in solid tumors.

[Slide.]

Results from both of the critical skeletal-related events analyses are listed here, the proportions analysis, as presented in the third column, followed by the estimated treatment difference and the 95 percent confidence intervals within that difference.

A negative number here is an estimate that favors the Zometa arm. The sixth column provides the hazard ratio for time to first skeletal-related event and then the confidence intervals. In this analysis, a number less than 1 is an estimate that favors Zometa. P-values are included for each analysis.

As I discussed earlier, each of these clinical trials suggests one or more important questions which I will summarize again in the next three slides. For study 010 in breast cancer and myeloma, we note that it is a single study of noninferiority design. The question for ODAC is do the totality of the data in the NDA provide support for this indication.

[Slide.]

In prostate cancer, the 4-milligram Zometa arm shows convincing results for both the primary and secondary skeletal-related endpoints. The 8-milligram arm shows no statistical difference from placebo. Again, two questions arise. First, considering both of the arms of the study, how convincing are these data that Zometa 4 milligrams is effective.

Second, prostate cancer produces blastic

bone metastases. When considering the efficacy of Zometa in prostate cancer, is it reasonable to also consider evidence of Zometa efficacy from studies of lytic bone metastases from other cancers?

[Slide.]

In patients with other solid tumors, the 4-milligram Zometa arm was statistical better than placebo in time to skeletal-related event but not by the proportions analysis. The 8-milligram Zometa arm was statistical better than placebo in both analyses. FDA believes that these data are convincing for the populations studied and received benefit. However, the population was heterogeneous. We want you to consider whether these data support approval for the treatment of all individual patients with all types of other solid tumors.

[Slide.]

For each of these studies, we want you, then, to put on the regulatory hat with us--if we have one in your size. You have to check with Stacy--and determine whether the data collectively meet the regulatory standard for demonstrating efficacy, substantial evidence from adequate and well-controlled investigations.

As I noted earlier, this means evidence from multiple clinical trials--it usually means evidence from multiple clinical trials--but very impressive and robust results from a single multicenter trial sometimes have been accepted.

You may find that one of these trials is so impressive that it supports approval without any support from another trial or you may find that, while a single trial is not convincing alone, you find the results of another study to be supportive.

We look forward to your advice on these matters.

DR. NERENSTONE: Thank you.

I am going to open the discussion now to the committee members. Just to check, Dr. Albain, can you hear us?

DR. ALBAIN: Yes; I can.

DR. NERENSTONE: Dr. Taylor, are you there?

DR. TAYLOR: Yes; I can hear you.

DR. NERENSTONE: Dr. Kelsen, are you with us?

DR. KELSEN: Yes; I am.

Committee Discussion and Vote

DR. NERENSTONE: Does anyone on the

committee have any questions? Actually, let's have some comments now. We are opening it up for discussion.

Dr. Lippman, I know that you had some comments that I think are very important to open up the discussion.

DR. LIPPMAN: I think that my comments were asked by subsequent people on the committee and answered so I don't have anything else to add to that. I think the issue of the 8/4 versus 4, we have heard all that we will know about that issue.

DR. NERENSTONE: I think that is an issue that is still a little problematic. Thinking about that, which is why is there not consistency in all the arms, I agree with Dr. Lippman that it seems like the sponsor has not really been able to adequately give us data about why, or explain why, it might be not consistent. It may be that they don't have the data.

Does the FDA have any thoughts about why there might be some inconsistency?

DR. WILLIAMS: We certainly looked to find some source of the problem. In my opinion, if you are looking for an excuse to explain, say, the drug works and why we find these things, the trials were

designed at 80 percent power. You expect one in five studies to be negative. I think the power of these studies was probably even less than that, getting the final effect size.

Depending on which analysis you see, you see trends in favor, and we don't see anything against. So my opinion is that, if the drug works and we have these results, it is probably chance.

DR. PAZDUR: One of the things I would like to bear in on this is we should look at the totality of data that is coming and not simply the clinical trials. One of the things that I urged the company to reiterate at this time, or people in their own minds to think of, is the pathophysiology of the disease, any potential differences in osteoblastic or osteolytic lesions, especially with the interaction of the bisphosphonates.

Would one expect from the underlying disease process and the mechanism of action of the bisphosphonates that one should see a difference in osteoblastic and osteolytic disease. Perhaps the company could address this again for the committee because, really, it isn't just the clinical trials. It is the totality of evidence that we must look at.

DR. SEAMAN: I am Dr. John Seaman from Novartis. I would like the slide with the information regarding all the trials that we have done with Zometa for hypercalcemia in bone metastases, et cetera.

[Slide.]

This slide depicts all the results of trials done in terms of Zometa in a malignant indication. On the left-hand side, you will see the Zometa hypercalcemia data in regards to the response rates for Zometa, 4-milligrams and 8 milligrams, versus pamidronate. These are in patients with bone metastases because they are probably a more reasonable patient population to look at because humoral is somewhat different.

As you can see, the proportion of patients having a response to Zometa in these treatment groups are somewhat variable. You see a 90 percent response for the Zometa 4-milligram treatment group, and 84 percent response for the 8/4 and a 80 percent response for pamidronate.

That is somewhat consistent when you look across the three trials that we have done in terms of bone metastases. There is a reflection that you see responses in terms of efficacy for prostate

cancer and for other solid tumors include non-small-cell lung cancer that is somewhat different when you look at the treatment groups.

If you look at the 4-milligram treatment group, for example, in the prostate-cancer patient population, there is a 33 percentage of patients having an SRE. For the 4-milligram group, it is around 38 percent. They are both reducing the portion of patients having an SRE although the 8/4 does not reach significance.

Somewhat of a different pattern sort of shows up in terms of the protocol 010 where the 8-milligram group is a bit more successful in having less SREs, 35 percent, and 38 percent in the 4-milligram treatment group.

Then you see, even in the other trials where we have seen noninferiority, you see variability in the data that you are looking at. Our feeling is the totality of data supports the fact that Zometa works across all these tumor types in terms of what is going on.

I think this is the first time we have an opportunity to look at all the results for all the trials we have done in a malignant setting with patients who have bone metastases.

DR. NERENSTONE: Thank you.

Dr. George?

DR. GEORGE: With respect to this issue of whether the results are contradictory, or the 4 and 8 business, it seems to me, in looking at all this, to try to synthesize it some, the obvious thing that I would do is just pool those results. If you had a situation--if your model ahead of time is that you can't come up with the plausible biological reasons why the 8 would produce a worse control in terms of the primary endpoint, then a sound statistical procedure is to sort of, in these restricted inference procedures--is to pool the data, to pool them and say, "This is the best estimate we can do of what the effect is."

I would do that on all these studies, if you want to try to get a handle on what that effect size really is. I think that is important because we have been focusing on a lot of the--we look at these confidence intervals but the effect size is really a key issue.

I like to think in terms of the number-needed-to-treat analyses. If the effect size is really, say, 8 percent like it seems to be in one of these, then the number needed to treat is 12,

12.5, to be precise, or something like you have to treat twelve or thirteen patients to reduce one SRE in one patient. The other eleven or twelve are treated for nothing--well, maybe not nothing, but at least with respect to the primary endpoint, that is what happens.

So then you have to assess is it worth it in that sense. So that is the way I tend to think of it. In other words, whether you do a formal pooling, just add them together, or pool them some other way, I think it is important to do that. That is the only way you can make sense of it.

But I have a fundamental point I wanted to address concerning--it is sort of a technical point but I think it is important with respect to what it is we are estimating. There have been two analyses, types of analyses, presented here with respect to the primary endpoint in the first event that occurs.

One is just simply the percentage of SREs that are observed in the specified time frame. The other is the time to that event. Now, there is a problem with both of these. It boils down to the fact--or it relates to the fact that you are in an area of a lot of competing risks. So what I would

have really like to have seen is something like cumulative-incidence kinds of curves.

Just to be clear, if you look at the percentage of events, the percentage of SREs that occur in this time frame, if you had no censoring at all, then those percentages would give you the same as the cumulative incidence. But, when you have censoring, they give you the wrong answer. They give you something different.

The answer you are getting when you look at those percentages of SREs is too low. It is too low. The cumulative incidence would actually be higher. On the other hand, if you do the time to the event and you censor the competing events, which I think is what was done on both the FDA's and the sponsor's analysis, then you get something that is too high.

So that is why you get this discrepancy. Maybe it is true that, if you did something else, if you did something like this cumulative incidence, that you would get the same qualitative answer but it is not guaranteed. So I don't know what that answer is. I would have liked to have seen that.

If you have already done it--

DR. SEAMAN: We have done it

DR. GEORGE: Then that would be interesting to see.

[Slide.]

DR. SEAMAN: Here is the cumulative incidence rate of SREs in all patients for the 4, 8/4 and pamidronate treatment group in terms of median time to first SRE. You can see that it is very similar in terms of the median time being around 397 days with the 4, 373 for the 8/4 and 370 for the 90 milligram.

DR. WILLIAMS: Could you clarify? Is that patients or all events, patients within event? When you say cumulative incidence rate, does that mean to the first event in a patient or all events?

DR. SEAMAN: It is the first-

DR. GEORGE: And do you have the same thing for the other--

DR. SEAMAN: Can I see the next slide, Slide 11?

[Slide.]

You can see that we have maintained the significance there with the median time, 314 not reached for the 8/4 and 185.

DR. GEORGE: Remind me; where was the time

point? If you do something vertically here--I just forgot the time that you looked at.

DR. SEAMAN: Nine months is the endpoint

DR. GEORGE: Nine months?

DR. SEAMAN: Yes.

[Slide.]

And then for 039, again, the cumulative incidence for 4-milligram treatment.

DR. GEORGE: So, trying to assimilate this quickly, qualitatively, you get the same results; is that correct?

DR. SEAMAN: Correct.

DR. SCHER: Excuse me. To me, it looks like the top two, the 8 and the placebo, seem to be running together.

DR. SEAMAN: It looks like exactly what we had if you look at the time to first SRE in that 039 data. They are running together the opposite way.

DR. BRAWLEY: That is consistent with the PSA data that was shown earlier as well for the 8/4.

DR. SEAMAN: Matt wants to address that a bit more. We talked about it a bit during the break and maybe he could say a little bit more

about that because we were talking about the 8/4 data a bit during the break, too, when we looked at the data and talked a bit.

DR. SMITH: I wish I could, with certainty, explain the difference between the 4 and 8/4 group in the prostate study. I don't think it is possible. So I think an honest attempt has been made and a thoughtful review by the FDA statisticians have done so.

I think about it in the following way. It is not just about reaching significance. It is also about the treatment effect. I like what Dr. George has said which is, if you think there is the possibility of imbalances or chance effect, then hold it against the drug and lump the less favorable arm in with the more favorable arm.

If you do that analysis, you have a 20 percent relative reduction--not absolute reduction, but 20 percent relative reduction in SREs in the combined 4 and 8/4 group compared to placebo. That is statistically significant.

By the way, that is exactly the same treatment effect you see in the pivotal placebo-controlled trials of pamidronate in breast cancer with 24 months follow up. You lump 18 and 19. So

breast-cancer patients with bone metastases treated with either chemotherapy or endocrine therapy, if you lump the studies together, at 24 months, you have about a 20 percent reduction in risk, relative reduction in risk.

So I think the treatment effect in prostate cancer is quite comparable to that you see in metastatic breast cancer. In the pooled analysis, trying to correct for any possible imbalances, you do maintain statistical significance with the primary effectiveness analysis.

I think there have been a lot of thoughtful attempts to provide other explanations, possible imbalances and such. When you do that, it does move the 8/4 group closer to statistical significance. It doesn't reach it. I am not sure what else could be done.

DR. NERENSTONE: Dr. Lippman?

DR. LIPPMAN: I would just like to clarify, Stacy, your comment. My question wasn't meant to be negative. It wasn't meant to be that the company couldn't explain it. I actually asked when the FDA presented. People that have really pored over this data and tortured it, I was just

trying to see if they had any sense of some of imbalances or thoughts that made it kind of--or people that know more about bone metastases than I do, if there was biological plausibility for this.

Certainly, in other areas, higher doses are not always better. Clearly, the 4-milligram is the cleanest arm and that data was convincing. The 8/4 shows the same trend, although it is not significant. So, again, I would just like to reiterate what Grant says. I can accept the fact that this was a chance finding. The totality of the data are very consistent.

I didn't mean--I thought the way you phrased it might have a sense that I was not happy with the answer or negative in any sense. I just was trying to see if people who looked at the data more closely had any other insight.

DR. BONOMI: Maybe I am missing something, but when we looked at the curves, when you showed the PSA levels, it was higher at baseline and it went higher throughout the study and that would suggest that their disease wasn't being controlled and that they were a worse group of patients.

DR. SMITH: I incompletely answered Dr. Raghavan's question about survival.

If you could bring up the overall survival slide. I think it is 28.

I misspoke by saying their median survival was about a year. It is, in fact, a bit longer than that. There were differences none of which reached statistical significance but there were differences in their survival.

I need the Kaplan-Meier survival curves, Slide 28 from my presentation.

[Slide.]

So the median survival in placebo was about fifteen months, 469 days. It was worse in Zometa, 8/4, 418, and best in Zometa 4. So there was trend towards better survival in 4 and the worst arm was the 8/4.

Now, in all of the other studies, we have looked at survival basically overlapped. So, if you look at overall survival, maybe as another way of thinking about potential imbalances, and recognize that we don't have a better explanation. I am trying to provide a reasonable explanation here.

If you look at that and say, this is an integrated way of looking at prognostic factors, perhaps this is the explanation. My guess is if

you pooled the survival for the 4 and 8/4, it looked exactly like placebo.

DR. NERENSTONE: Dr. Albain, did you have a question?

DR. ALBAIN: No.

DR. NERENSTONE: Dr. Temple?

DR. TEMPLE: I wanted to ask Steve how much explanation of these kinds of differences is needed. The power of these studies isn't infinite. The p-values for the most favorable results are fairly close to 0.05. If the true difference is what it was in that study, your chance of replicating it on another study is only modest, at best.

So is there anything here to explain except that the effect isn't very big?

DR. GEORGE: I would say no. I think the results here are pretty clear, if you are trying to get my conclusion ahead of time. It is pretty clear. The way I get them is to pool those results together. I see attenuation of the effect of the most extreme one because I think it is probably random variation. I haven't heard any other plausible reason.

I have heard some things thrown out that

might have contributed but there is no real good evidence that there is anything there. So it is fairly straightforward for me in that sense.

DR. NERENSTONE: I just wanted to ask--or talk to Dr. Williams. I think that three of the studies are pretty--to my mind, the answers are pretty--or two of the studies-- are pretty clear. But, going back to the solid tumor, which is a little bit more of a hodgepodge of studies, and some concern about the heterogeneity of the patient population, I guess, from a clinical point of view, I would look at the statistical numbers there.

There, of interest, is that the p-values are significant; that is, the p-values for the Zometa 4 milligrams in the time to first SRE, which is your preferred analysis, was significant at the 0.02 level and both the difference in the proportion as well as the time to first SRE are significant for the 8-milligram.

The argument about heterogeneity of the patient population, I think, is important. Again, if you postulated that perhaps there would be a difference of what it is doing or how tumor types are going to act on the bone, and if they didn't have a significant p-value, that would be raised.

The fact that these are significant, in my mind, suggests that the mechanism either is the same or is affected in the same positive way. To my thinking, I don't have a problem with that. I think, from a clinical point of view, to have a phase III trial in metastatic cervix cancer to the bone is not going to happen and, in fact, this data suggests that those patients would benefit from this kind of treatment.

I just wanted to open this up to the committee because I think is the most problematic study.

Dr. Lippman?

DR. LIPPMAN: Again, this gets at what Rick raised. From what I have heard, and not being an expert on bone physiology, it seems as thought the pathophysiology of the lytic and blastic lesions, the aspect is similar. Unless there is really a biological reason to think that it is different, I think it may be reasonable to include them all as one for the reasons you mentioned, and Stacy, that it is really not going to be practical or possible to do single-site definitive trials.

So there would have to be some real biologic reason not to, and I haven't heard that.

DR. NERENSTONE: Dr. Temple.

DR. TEMPLE: As Grant said, we always wonder how quickly to generalize any putative common mechanism. Anybody can make up a mechanism, you know, and it will always be plausible because they wouldn't offer anything silly. So the question is how much replication, how much verification, do you need.

As Grant said, the division thought, well, you have got prostate, you have got breast, you have got a variety of solid tumors. That is getting to the point where you might consider this to be a generalizable finding. That is obviously one of the things we want to ask everybody, how plausible that seems, plus all the other data from drugs in the class. You bring all of that.

DR. NERENSTONE: Dr. Przepiorka?

DR. PRZEPIORKA: I think there is a lot of data to suggest that statistically we are seeing something. But I guess the question on the table is is there substantial evidence to support approvals for these indications. We are clearly not treating the primary cancer, and the survival statistics pretty much show that we are not treating the primary cancer.

The quality-of-life indicators demonstrate no benefit for the drug. The median time to SREs are the same in the breast-cancer trials so you can't really say anything since that is an equivalency trial. But, for the solid-tumor trial, the reduction of median time to SRE is only two months. So the question is, in the clinic, is that going to make a difference.

The point reduction in SREs at nine months or one year, I have heard conflicting data and it wasn't on the slide, is 8 percent. Is 8 percent enough to really say that this is substantial clinical evidence for a benefit for these patients?

I would like to hear anybody else's comments about that, too.

DR. NERENSTONE: Dr. George

DR. GEORGE: I am not going to address clinically whether it is, but it relates to what I mentioned earlier about the--if it is true. Let's just assume, for the moment, that 8 percent is the true difference. I mean, really, if you give this agent, you will get 8 percent less SREs in the time frame specified. That is the main thing you are looking at. We are not considering all the other endpoints right now.

That means that you have to treat twelve or so patients in order to get that one benefit. So eleven are not getting any benefit, in that sense. They might be getting something else if there is some other benefit, but I didn't see any other benefit.

So what you are getting is those eleven patients or so were getting treated with something that is not doing them any good. So, is it worth it? I don't know regulatory--

DR. PAZDUR: Could I clarify something, Donna? When you are talking about significance here or substantial evidence, what you are really talking about is is this of clinical importance or clinical significance.

The way, really, the questions were raised and what we were thinking of is more substantial evidence of a drug effect. There are, really, two kind of separate issues, perhaps. One is does it make sense from a clinical point of view this two months or whatever, X months, may be. That is a clinical question.

The other one is substantial evidence, is that reproducible, is it a reliable statistical point of view. So there are two kind of different

issues come into play here, I think.

DR. NERENSTONE: Dr. Przepiorka?

DR. PRZEPIORKA: I was actually thinking about that in the same way as well because, clearly, if the effect is so marginal, a second study may not show a benefit at all.

DR. NERENSTONE: The sponsor would like to say something.

DR. SEAMAN: I think if you take into consideration the 8 percent, that is probably correctly, if you are just counting the first event. But, if you wouldn't mind, let me show you all the events, if you count all the events. The only way you can look at that is in a multiple-event analysis.

It is not in any of your slides, but let me just give you an idea how many events occurred in this patient population over the course of the trial and just give you the numerical numbers.

May I have those slides?

If you remember back to Dr. Coleman's slide where he showed the hundreds and hundreds of events that took over the 24 month period. Let's take a look at what we saw, too. That 8 percent is just a first event, whether it be proportion or--

[Slide.]

This is for protocol 010. During the course of that thirteen-month evaluation, there were 808 SREs in terms of Zometa 4 and pamidronate at 849. These are the types of things that took place during that time frame. So it is substantial. It is pretty similar to what we are seeing. So we are just talking about an 8 percent reduction.

Now, we don't have a placebo group in this but let's look at the next set of slides for 011 and 039.

[Slide.]

You can see, again, here, that, over that nine-month time frame, there are a number of these events occurring in the placebo treatment group, quite a few, 275, if you included hypercalcemia. You were just counting that first event. In each treatment group, you are having an impact. In the treatment group, you are seeing an impact on that.

[Slide.]

Finally, in protocol 039, again you see that there are a substantial number of events we are not counting. So there are a whole host of other events that we are taking into consideration.

If you look at the multiple-event analysis in terms of protocol 011 and protocol 039, it is a 25 to 27 percent reduction in these events rates.

DR. NERENSTONE: I think, Donna, one of your questions is more a more philosophical one, which is how meaningful clinically is this drug. I think no one who treats patients is going to say this is a home run but it probably is a small improvement.

Certainly, for those of us who treat a lot of breast-cancer patients, showing that Zometa is not worse--and you might want to debate that--but is probably not worse than pamidronate, getting patients out in fifteen minutes rather than two hours definitely is going to add to their quality of life and the patients will tell you that. And that is a big deal.

So that study, in itself, I think, as much as we don't like "me, too" drugs, does provide an advantage, just on the basis of that alone.

MR. KAZMIERCZAK: I would agree with that. Fifteen minutes instead of two hours certainly does make a difference when you are a patient. I agree.

DR. NERENSTONE: Dr. Temple?

DR. TEMPLE: Of course, if the effect

isn't worth anything, you can avoid the fifteen minutes and the two hours.

It is worth remembering that if you look at the absolute percent difference--I mean, there is a constant debate about this and Steve is trying to do this, how many people do you have to treat to benefit anybody. In some settings, hypertension and things like that, we are accustomed to looking at the percent reduction in bad events when the actual reduction might be only 1 or 2 percent per year. But that is because the events are considered so very bad.

In these, I guess not all of the events are really horrible, but some of them probably are. So it is worth at least considering the hazard-ratio part of it, too, which gives you some sense of the relative reduction in the nasty events and which shows a larger effect, obviously, than the absolute reduction of roughly double.

DR. NERENSTONE: Dr. George?

DR. GEORGE: Just as follow up. Actually, I don't know if it was addressed here. Maybe someone knows it. Grant, I think, mentioned something about it earlier. The endpoint, the SRE, is a very heterogeneous collection of events, some

of which are treatment driven and some of which are biologically based.

I have been just assuming that this is a widely accepted endpoint in this area, but what is the genesis of this endpoint?

DR. WILLIAMS: I am sure Dr. Seaman could comment on this too, but, as I recall, the company developed this endpoint for the Aredia trials and certainly, we were involved. The basic idea was to try to capture the very different kinds of morbidity that seemed to be about of the same significance. There was a big debate, do you put hypercalcemia on here, and we steadfastly said no, that this is something different, of a different nature, that you could treat later.

I think that, as it happened, the bone events ended up being a little different than we expected. I think we were probably thinking about long-bone fractures and it ended up being a lot of compression fractures, of less significance, perhaps, than we initially anticipated.

But I think we really have come to think of the radiation therapy to bone to be a reasonable sort of an integrator of what--a physician, I don't think, just willy-nilly, goes out and puts the

patient in for a course of radiation therapy that ended in a blinded trial where they don't know which arm is getting which.

They are making that commitment usually for something significant. So, even though they are different in nature, we felt like they were about of the same significance and I think we felt comfortable over the past seven or eight years, perhaps, with this event.

I don't know that it has been used anywhere outside of the regulatory environment.

DR. NERENSTONE: Dr. George

DR. GEORGE: Along those lines, the consistency of these studies, if you look at this first page you gave us, if you do that pooling that I was talking about across the treatments, it is really remarkable that the proportion of patients with an SRE, it would 36 percent in the treated group pooled in the prostate-cancer study, in the placebo, 44 percent.

In the solid tumors, the lung cancer and others, exactly the same thing, with a different time period but in different kinds of events and patterns. But, overall, you get precisely the same point estimates. That is with that 8 percent

effect.

DR. NERENSTONE: Dr. Bonomi?

DR. BONOMI: From a clinical perspective, if you prevent one patient out of twelve from having severe pain or from having a pathologic fracture, I think that is very clinically relevant. Even though we can't pick it up in the quality of life, all the patients are in one pool, that really has a huge impact on the quality of life, if you have terrible pain. Certainly, if you have a fracture, it is much worse.

DR. NERENSTONE: Dr. Raghavan?

DR. RAGHAVAN: I would like to change gears just a little bit. It comes back to Matt Smith's late response to my question. You know, one of the things that I think is important--because one senses there is a consensus around the table that these are relatively straightforward decisions. It is the fine tuning that we are spending the time on.

So I, with that in mind, took the liberty of looking at the package insert. It does strike me that, in the context of prostate cancer, for someone who does see a lot of prostate cancer and bad prostate cancer that is aggressive, as a

clinician, I am not sure that I know where this drug should find its place.

I think everything that has been said about reducing the pain for patients is true. I think it is good to do that, but I am not sure that what I have heard today will tell me how to apply it in clinical practice. So, if it does happen that this gets approval, I would say to the FDA, you want to spend some time with the company looking at the development of the package insert and getting the wording right.

We know that people tend to telescope from meetings such as this. I could imagine that there could be tens of thousands of patients who have radical prostatectomies who go on this straight away "to prevent bone complications."

We know that people use drugs in strange ways. Now, even within the context of what we have heard, I am absolutely convinced that a very good thing to be is--I mean, it is not a good thing to be stuck with prostate cancer, but it seems to get into this trial is a good thing because every arm has good survival.

I think what that really tells us is it is a very heterogenous group. In the real world, the

median survival for prostate cancer is short. Skeletal-related events occur more commonly than even in the placebo-treated group here. It probably means the doctors have managed them well. I don't take that away from the treating team, but I do think there is case selection, as I said before.

Median weight seems to be--well, half the patients have a weight between 80 and 130 kilograms. That is pretty big for a patient with prostate cancer. There is not a lot of anemia. There is not a lot of hydronephrosis. There are not a lot of the things that you would expect to see. So what I think we have got in the definition of patients going into the trial is a mix of people who have had a bit of chemotherapy for a range of reasons.

People are on hormones, off hormones, and so on. So, while I don't think that detracts from the importance of the product, I think the FDA is going to need to spend some time on the package insert. It may well behoove the company to look at sets of patients like those who present with more significant symptoms than require codeine only.

The vast majority of patients with

prostate cancer and bone metastases have severe pain and major problems. So I think they have picked a good group, which is fine, but in the further development of the drug, it might be nice to encourage them to look at some of the tougher cases.

DR. NERENSTONE: Dr. Loeher?

DR. LOEHER: I just want to echo what Derek said. I mean, a nice clean study which would have answered a lot of questions is primary treatment of hormonal-sensitive patients to do orchi-activity or do LHR-antagonist with or without this. Then you would be able to get removal out of these variables and find out exactly how to do that. So I would encourage the company to pursue that.

The other question I had, I guess along that line, and picking up on what Donna said, is what is the subset of patients that are going to benefit. Do we need to treat all of these people or can we identify them? The question I have, and I don't understand curves and stuff, but you had this urinary telopeptide-creatinine ratio. Is this useful in terms of predicting who will respond and who will not respond in terms of outcome?

DR. SEAMAN: I will have Rob Coleman answer that who is very familiar with a lot of the things that have been done over the years and it is somewhat in its infancy.

DR. COLEMAN: Rob Coleman. Most of the data with N-telopeptides is actually from the breast-cancer literature. It is a small series so it is difficult to add a lot of weight to it, but it seems that what we should be trying to do is normalize bone resorption. The way we measure that is, obviously, with one of these bone markers.

There are some patients who you won't normalize bone resorption even with a bisphosphonate for reasons that are not very well explained. So I think we do have to look at trying to use the markers to pick out those patients who are unresponsive because, clearly, bisphosphonates are not a panacea. They are an improvement but they are not a panacea.

Trying to use the markers to predict who is going to respond in the first place--for instance, if you have absolutely normal bone resorption, why add in the bone-resorption-inhibitor on top? So there may be people who you don't need to treat or there may be people who are

resistant and our hope is that the markers will sort this out

Obviously, there is as huge database of information that will be analyzed over the coming months to try and dissect that out, but that is the theory behind it. But there isn't a sort of internationally approved set of response criteria that we could use as of today.

DR. NERENSTONE: Other comments from the committee? Dr. Kelsen?

DR. KELSEN: No; I have no more comments at this point.

DR. NERENSTONE: Dr. Albain?

DR. ALBAIN: Yes. I wondered if we could have a little bit of discussion about the labeling in renal function and what--

DR. NERENSTONE: We are losing you, Kathy. Hold on just a minute. Try again.

DR. ALBAIN: I wondered if we could have a little discussion about the labeling and the pretreatment renal function as well as monitoring. Are we going to recommend that this not be given for creatinine clearances less than 30 or could we have a little more discussion about that?

DR. WILLIAMS: We are having discussions

internally on that matter. I don't think we have made up our mind what to recommend. Certainly, this is renally excreted and there seems to be a relationship between the creatinine and toxicity and AUC and toxicity. But whether or not you would recommend treatment outside of the range of the study, that is still a point for debate, I think. We probably won't have that debate here.

DR. NERENSTONE: Any other questions, Dr. Albain?

DR. ALBAIN: Just thinking, when we give pamidronate, as a rule, in practice, we don't routinely--or many places do not get a serum creatinine before each dose. What we have seen today would seem to indicate that you probably should as much as you should with this agent.

Is that going to be a strong suggestion that it be done? It was alluded to during the presentations. How necessary is that?

DR. SCHER: I think you are right that initially the nephrotoxic nature of pamidronate was not that obvious as imparted to us clinicians, which it was at the time. I can't make a comment on that label at this point but, as Grant said, the exact labeling of this drug will be under

discussion. Clearly, we will be recommending, if Zometa is approved, that creatinine be closely monitored and there will be some comment on level of renal function. But that has to be discussed further.

DR. ALBAIN: Just to follow that up a little bit further because these patients routinely will be just coming in including visits for the agent without physician input on each and every dose. If we follow the guidelines of the clinical trial for Zometa, it is a lot more involved.

You hold it. You wait until it decreases to a certain fraction, et cetera. So it may change the national practice standards of how we give these agents based on what you decide.

DR. NERENSTONE: To follow that up, are you going to recommend the vitamin D and calcium which, I guess, all patients on these studies go on and was sort of news to me.

DR. WILLIAMS: We generally do put in the label the way it is done in the study. We have a noninferiority study which seemed very similar with the amount of toxicity to Aredia. We just happen to have the sponsor for Aredia here in the same room. I would think that we would generally want

that label to be pretty similar regarding this.

DR. NERENSTONE: Dr. Kelsen, did you have any questions?

DR. KELSEN: No additional questions.

DR. NERENSTONE: Dr. Taylor, do you have any questions?

DR. TAYLOR: Not right now.

DR. NERENSTONE: I will take that as a no.

Dr. Lippman?

DR. LIPPMAN: I just wanted to bring up again, just to make sure we brought some closure, albeit with, maybe, not the perfect answers, but FDA, Bob, everyone raised the issue of the blastic versus lytic. It came up again in Pat's questions about can we dissect who would respond or not. Since one might have thought that the biggest predictor might have been whether it is blastic or lytic and that doesn't seem to be the case, is there any more discussion? I think Bob left it with, well, you can always come up with biologic plausibility.

I think we have heard one mechanism. We haven't heard any others that would dispute it and we see results in the two tables, Grant, that you put on this page which show very similar results in

prostate and the others.

So I don't know that we have any information or anything else to say that it shouldn't be used in both. I just don't know. Have we resolved that? Because it is one of the major questions that you raised and one of the questions on the sheet. Is there anything that you want to discuss?

DR. WILLIAMS: You have heard the evidence, preclinical and clinical. It is your discussion.

DR. PAZDUR: Perhaps you will resolve it with your vote.

DR. NERENSTONE: Dr. George

DR. GEORGE: Along those lines, one other issue I haven't completely resolved in my own mind is the myeloma data with respect to the first study because the main thing that concerns me about that still is that difference with the Aredia effect--not the effect because we don't have a placebo, but the Aredia results--in the new study and the old. It is sort of indirect evidence that there is not a constancy here but--maybe very indirect, but there were some prognostic factors that seemed to be different.

But I am still a little worried about that. After saying I favor pooling generally, now I am sort of backtracking a little bit, got a little worried about the fact that breast cancer seems very clear, clear-cut. That is nice. And the myeloma, I am wondering whether that evidence is really there strong enough.

[Slide.]

The only thing I could think to do was to try to find patients that were similar within the old trial and see what estimate effect we had. It seemed to be, if anything, greater. So that is all I could think to do to examine that question. It seemed to be clear that they were a more aggressive disease and one could wonder is it so aggressive that we are going to have no effect on it.

But, in looking back at similar patients with what appeared to be more aggressive disease, earlier time since diagnosis, the effect seemed, if anything, more, the Aredia versus placebo effect. So I think that is about all we could do.

DR. NERENSTONE: Dr. Raghavan?

DR. RAGHAVAN: I would like to respond to Scott Lippman's question. I think that it is only one trial but the differences are actually quite

compelling, not withstanding the caveats that I put in, in prostate cancer. That really is an absolutely blastic-metastasis-dominated disease. I think they showed it somewhere in the stuff we have looked at today that there were a tiny proportion of mixed sclerotic and lytic.

But, for practical purposes, prostate cancer, in the board questions, comes up. You see a picture of blastic metastasis. So I was pretty impressed with the prostate as a paradigm of blastic disease so it didn't leave me feeling too uncomfortable about that issue.

DR. NERENSTONE: Dr. Lippman?

DR. LIPPMAN: I think that was sort of the point, that we have sort of the biologic plausibility, the only mechanism that we have. And we have consistent clinical results that also support efficacy. So, again, I don't know that we have anything else to resolve it, but there is no other data to have to suggest that isn't active in that setting.

DR. NERENSTONE: Mr. Kazmierczak?

MR. KAZMIERCZAK: I guess I would have been a participant in your clinical trial if I could because I am a patient with a rising PSA

right now. I hope I am one of the one in twelve. One in twelve is certainly better than none in twelve. Thank you.

DR. NERENSTONE: If we could turn now to the questions. We have all seen the first page. I am not going to go over that.

For new drug approval, substantial evidence of efficacy from adequate and well-controlled investigations is required. Evidence from multiple clinical trials is usually submitted but robust results from a single multicenter trial have been accepted.

We are going to consider whether the results from trials fulfill the regulatory requirement. So the first study we are going to look at is study 010 in breast cancer and myeloma. In that study, 44 percent of Aredia patients had an SRE on study versus 46 percent of Zometa patients.

Using the conservative two-95-percent-confidence-interval method, the FDA calculates that Zometa retains at least 49 percent of Aredia's efficacy demonstrated historically in comparison to placebo.

The first question, do other studies, 011 and 039, provide supportive evidence for Zometa's

efficacy in breast cancer and myeloma.

DR. SEAMAN: The numbers are reversed, 44 for Zometa, for Aredia 46 percent.

DR. NERENSTONE: Okay. Thank you. So it is 46 percent of the Aredia and 44 percent for Zometa. I am going to have to see a show of hands and then I will ask for our participants at the remote locations by name. So, first we are going to go around the table. Do the other studies provide supportive evidence for Zometa's efficacy in breast cancer and myeloma?

Dr. Kelsen?

DR. KELSEN: Yes.

DR. NERENSTONE: Dr. Albain?

DR. ALBAIN: Yes.

DR. NERENSTONE: Dr. Taylor?

DR. TAYLOR: Yes.

DR. NERENSTONE: Dr. Raghavan?

DR. RAGHAVAN: Yes.

DR. NERENSTONE: Dr. George

DR. GEORGE: Yes.

DR. LIPPMAN: Yes.

MR. KAZMIERCZAK: Not being a clinician, I will abstain.

DR. PRZEPIORKA: Yes.

DR. NERENSTONE: Yes.
DR. BRAWLEY: Yes.
DR. PELUSI: Yes.
DR. NERENSTONE: It is ten yes and one abstention.
Part b; is there substantial evidence from adequate and well-controlled investigations of Zometa, 4 milligrams, efficacy in breast cancer and myeloma?
Dr. Kelsen?
DR. KELSEN: Yes.
DR. NERENSTONE: I'm sorry; first of all, are there any other comments from the committee? Okay.
Dr. Kelsen?
DR. KELSEN: Yes.
DR. NERENSTONE: Dr. Albain?
DR. ALBAIN: Yes.
DR. NERENSTONE: Dr. Taylor?
DR. TAYLOR: Yes.
DR. NERENSTONE: Dr. Raghavan?
DR. RAGHAVAN: Yes.
DR. NERENSTONE: Dr. George
DR. GEORGE: Yes.
DR. NERENSTONE: You can now go around the

table. I don't have to call your name.

DR. LIPPMAN: Yes.

MR. KAZMIERCZAK: Yes.

DR. PRZEPIORKA: Yes.

DR. NERENSTONE: Yes.

DR. BRAWLEY: Yes.

DR. PELUSI: Yes.

DR. NERENSTONE: Eleven yes.

The next page. Study 039 in prostate cancer. Zometa studies 010 and 011 have evaluated Zometa efficacy in predominantly lytic metastases. Can results from these studies provide supportive evidence for Zometa's efficacy in prostate cancer which produces predominantly blastic bone metastases? Further comments from the committee? I think we have talked about this.

Dr. Kelsen, do you want to start us?

DR. KELSEN: Yes; I will say yes.

DR. NERENSTONE: Dr. Albain?

DR. ALBAIN: Yes.

DR. NERENSTONE: Dr. Taylor?

DR. TAYLOR: Yes.

DR. RAGHAVAN: Yes.

DR. GEORGE: Yes.

DR. LIPPMAN: Yes.

MR. KAZMIERCZAK: Yes.
DR. PRZEPIORKA: Yes.
DR. NERENSTONE: Yes.
DR. BRAWLEY: Yes.
DR. PELUSI: Yes.
DR. NERENSTONE: Eleven yes.
Part b; is there substantial evidence of Zometa, 4 milligrams, efficacy in prostate cancer from adequate and well-controlled investigations? Any further comments?
Dr. Kelsen, you are doing such a good job. Would you like to start?
DR. KELSEN: Yes.
DR. NERENSTONE: Dr. Albain?
DR. ALBAIN: Yes.
DR. NERENSTONE: Dr. Taylor?
DR. TAYLOR: Yes.
DR. RAGHAVAN: Yes.
DR. GEORGE: Yes.
DR. LIPPMAN: Yes.
MR. KAZMIERCZAK: Yes.
DR. PRZEPIORKA: Unfortunately, I have to say no. The reason I have to say no is because, as was pointed out, there may be a difference between the patient groups because of the survival

difference in the Zometa, 4-milligram, dose so I am not sure I could actually draw this conclusion as much as I would like to.

DR. NERENSTONE: Yes.

DR. BRAWLEY: For 4 milligrams, yes.

DR. PELUSI: Yes.

DR. NERENSTONE: The vote is ten yes and one no.

For study 011 in other solid tumors. Analysis from both the 4-milligram and 8-milligram Zometa arms of study 011 support the efficacy of Zometa. Do you agree with FDA that these results provide substantial evidence of Zometa, 4 milligrams, efficacy in the population studied? Any comments?

Dr. Kelsen?

DR. KELSEN: Yes.

DR. NERENSTONE: Dr. Albain?

DR. ALBAIN: Yes.

DR. NERENSTONE: Dr. Taylor?

DR. TAYLOR: Yes.

DR. RAGHAVAN: Yes.

DR. GEORGE: Yes.

DR. LIPPMAN: Yes.

MR. KAZMIERCZAK: I abstain.

DR. PRZEPIORKA: Yes.

DR. NERENSTONE: Yes.

DR. BRAWLEY: Yes.

DR. PELUSI: Yes.

DR. NERENSTONE: Ten yes and one abstention.

The sponsor's proposed indication includes "treatment of osteolytic, osteoblastic and mixed bone metastases of solid tumors." This indication infers treatment as indicated for patients with bone metastases from all solid tumors irrespective of the primary tumor. Do you agree with this proposed indication?

Further comments? Dr. Loehrer?

DR. LOEHRER: I have some concerns about how this may be used for prostate cancer, patients who are not hormone refractory who have bone mets may get primary hormonal therapy and do extremely well. The way this indication is listed, it goes beyond what the studies were designed.

DR. WILLIAMS: This is actually referring just to the other solid-tumor group, but we will take that into consideration when we are thinking about the prostate indication.

DR. NERENSTONE: Other comments? For the

vote, Dr. Kelsen?

DR. KELSEN: Yes.

DR. NERENSTONE: Dr. Albain?

DR. ALBAIN: Yes.

DR. NERENSTONE: Dr. Taylor?

DR. TAYLOR: Yes.

DR. RAGHAVAN: Yes.

DR. GEORGE: Yes.

DR. LIPPMAN: Yes.

MR. KAZMIERCZAK: Yes.

DR. PRZEPIORKA: Yes.

DR. NERENSTONE: Yes.

DR. BRAWLEY: Yes.

DR. PELUSI: Yes.

DR. NERENSTONE: Eleven yes.

There is a last sentence. Please provide suggestions for wording of the indication section or the clinical-trials section of the Zometa labeling with regard to this issue.

Do you have enough discussion now?

DR. WILLIAMS: Yes. It wasn't clear where the discussion would go, whether you were going to say, "all solid tumors except," this or that. But I think you have addressed that.

DR. NERENSTONE: I would like to thank

everybody for their attendance. We will meet again at the end of February, February 27.

Thank you.

DR. TEMPLETON-SOMERS: Thank you Kathy, Sarah and David for pioneering for us. Thanks.

[Whereupon, at 2:00 p.m., the meeting was adjourned.]