



U.S. Food and Drug Administration

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1                               FOOD AND DRUG ADMINISTRATION  
2                               CENTER FOR DRUG EVALUATION AND RESEARCH  
3                               ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS  
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7                               THURSDAY, AUGUST 13, 2009  
8                               8:00 a.m. to 5:00 p.m.  
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11                              Hilton Washington, D.C./Gaithersburg  
12                              620 Perry Parkway  
13                              Gaithersburg, Maryland  
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1                   P R O C E E D I N G S

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3                   DR. CARSON: This is the meeting of the  
4   FDA's Advisory Committee for Reproductive Health  
5   Drugs. My name is Sandy Carson. I'm a professor at  
6   Brown University and chair of this committee.

7                   I would like to begin by first thanking the  
8   committee members. This is a time of lots of  
9   vacations, difficult air travel, and you have really  
10  been gracious enough to accept our invitation and  
11  done, I'm sure, your preparation. And we thank you  
12  very much for being here. I would like the committee  
13  to introduce themselves and let's begin with FDA  
14  staff.

15                  DR. PAZDUR: Richard Pazdur, Office of  
16  Oncology Drug Products.

17                  MS. BEITZ: Julie Beitz, Office of Drug  
18  Evaluation three.

19                  DR. BENSON: George Benson, Deputy Director  
20  of the Division of Reproductive and Urologic Products.

21                  MS. DEMKO: Suzanne Demko, Medical Reviewer  
22  Division of Biologic Oncology Products.

1 DR. KEHOE: Theresa Kehoe, Clinical Team  
2 Leader of Division of Reproductive and Urologic  
3 Products.

4 DR. COLLINS: I'm Michael Collins. I'm at  
5 the National Institutes of Health.

6 DR. ROSEN: Cliff Rosen, I'm an  
7 endocrinologist at Maine Medical Center Research  
8 Institute.

9 DR. UZEL: Gulbu Uzel, immunologist and a  
10 pediatric rheumatologist at The National Institutes of  
11 Health.

12 DR. BENNETT: John Bennett from NIAID-NIH  
13 Bethesda.

14 DR. EMERSON: Scott Emerson a  
15 biostatistician from The University of Washington in  
16 Seattle.

17 MS. BHATT: I'm Kalyani Bhatt; I'm the  
18 Designated Federal Official.

19 DR. JOHNSON: Julia Johnson, chair of OB-GYN  
20 University of Massachusetts.

21 MR. GOOZNER: Merrill Goozner, I'm an  
22 independent writer and consultant for consumer groups

1 on health care related issues.

2 DR. NELSON: Larry Nelson, reproductive  
3 endocrinologist, intramural research program NIH.

4 DR. MARGOLIS: David Margolis, I'm in the  
5 Department of Dermatology and the Department of  
6 Biostatistics and Epidemiology at the University of  
7 Pennsylvania.

8 DR. BUZDAR: Aman Buzdar, from the  
9 University of Texas, MD Anderson Cancer Center. I'm  
10 the medical oncologist with interest in breast cancer.

11 DR. MORTIMER: Joanne Mortimer, I'm a  
12 medical oncologist with an interest in breast cancer,  
13 City of Hope.

14 DR. RICHARDSON: Ron Richardson, medical  
15 oncologist Mayo Clinic, Rochester, Minnesota.

16 DR. GULLEY: James Gulley, medical  
17 oncologist with an interest in prostate cancer at the  
18 National Cancer Institute.

19 MS. SOLONCHE: Martha Solonche, patient  
20 representative from New York City.

21 DR. GUT: Robert Gut, Executive Medical  
22 Director at Novo Nordisk, I'm an industry

1 representative.

2 DR. CARSON: Thank you. And also our  
3 transcriber today is Robin Boggess.

4 There are a few things that we must read  
5 into the record. For topics such as those being  
6 discussed at today's meeting, there are often a  
7 variety of opinions, some of which are quite strongly  
8 held. Our goal is that today's meeting will be a fair  
9 and open forum for discussion of these issues and that  
10 individuals can express their views without  
11 interruption. Thus, as a gentle reminder, individuals  
12 will be allowed to speak into the record only if  
13 recognized by the chair. We look forward to a  
14 productive meeting.

15 In the spirit of the Federal Advisory  
16 Committee Act and the Government in the Sunshine Act,  
17 we ask that advisory committee members take care that  
18 their conversations about the topic at hand take place  
19 in the open forum of the meeting.

20 We are aware that members of the media are  
21 anxious to speak with the FDA about these proceedings.  
22 However, FDA will refrain from discussing the details

1 of this meeting with the media until its conclusion.  
2 Also, the committee is reminded to please refrain from  
3 discussing the meeting topic during breaks or during  
4 lunch. Thank you.

5 Then, also, I would like to remind everybody  
6 to silence your cell phone if you have not already  
7 done so, and I would like to identify the FDA press  
8 contact who is Pat El-Hinnawy.

9 There you are. Thank you.

10 Let me ask Kalyani to read the conflict of  
11 interest statement.

12 MS. BHATT: Good morning. The Food and Drug  
13 Administration, FDA, is convening today the meeting of  
14 the Advisory Committee for Reproductive Health Drugs  
15 of the Center for Drug Evaluation and Research under  
16 the authority of the Federal Advisory Committee Act of  
17 1972.

18 With the exception of the industry  
19 representatives, all members and temporary voting  
20 members of the committee are special government  
21 employees, SGEs, or regular federal employees from  
22 other agencies and are subject to federal conflict of



1 interest laws and regulations.

2           The following information on the status of  
3 this committee's compliance with federal ethics and  
4 conflict of interest laws covered by, but not limited  
5 to, those found at 18 USC Section 208 and Section 712  
6 of the Federal Food, Drug and Cosmetic Act, FD&C Act,  
7 is being provided to participants in today's meeting  
8 and to the public.

9           FDA has determined that members and  
10 temporary voting members of this committee are in  
11 compliance with federal ethics and conflict of  
12 interest laws. Under 18 USC Section 208-B3, Congress  
13 has authorized FDA to grant waivers to special  
14 government employees who have potential financial  
15 conflicts when it is determined that the agency's need  
16 for a particular individual's service outweighs his or  
17 her potential financial conflict of interest.

18           Under Section 208, Congress has authorized  
19 FDA to grant waivers to regular government employees  
20 who have potential financial conflicts when it is  
21 determined that the financial interest is not so  
22 substantial to be likely to affect the integrity of

1 the individual's service to the government.

2 Under section 712 of the FD&C Act, Congress  
3 has authorized FDA to grant waivers to special and  
4 regular government employees with potential financial  
5 conflicts when necessary to afford the committee  
6 essential expertise.

7 Related to the discussion of today's  
8 meetings, members and temporary voting members of the  
9 committee who are special and regular government  
10 employees have been screened for potential financial  
11 conflicts of interest of their own, as well as those  
12 imputed to them, including those of their spouses or  
13 minor children and for purposes of 18 USC Section 208,  
14 their employers. These interests may include  
15 investments, consulting, expert witness testimony,  
16 contract grants, CRADAs, teaching, speaking, writing,  
17 patents and royalties, and primary employment.

18 For today's agenda the committee will  
19 discuss and make recommendations regarding the new  
20 biologic license application for Prolia for the  
21 proposed indications of the treatment and prevention  
22 of osteoporosis in postmenopausal women and the

1 treatment and prevention of bone loss in patients  
2 undergoing hormone ablation for prostate or breast  
3 cancer. This is a particular matter involving  
4 specific parties.

5           Based on the agenda and all financial  
6 interests recorded by the members and temporary voting  
7 members of the committee, it has been determined that  
8 interest in firms regulated by the Center for Drug  
9 Evaluation and Research present no potential for a  
10 conflict of interest.

11           To ensure transparency, we encourage all  
12 standing committee members and temporary voting  
13 members to disclose any public statements that they  
14 have made concerning the product at issue.

15           With respect to FDA's invited industry  
16 representatives, we would like to disclose that  
17 Dr. Robert Gut is participating in this meeting as a  
18 non-voting industry representative acting on behalf of  
19 regulated industry. Dr. Gut's role at this meeting is  
20 to represent industry in general and not any  
21 particular company. Dr. Gut is employed by Nova  
22 Nordisk.

1           We would like to remind members and  
2 temporary voting members of the committee that if the  
3 discussions involve any other products or firms not  
4 already on the agenda for which an FDA participant has  
5 a personal or imputed financial interest, the  
6 participants need to exclude themselves from such  
7 involvement and their exclusion will be noted for the  
8 record. FDA encourages all participants to advise the  
9 committee of any financial relationships that they may  
10 have with any firm at issue. Thank you.

11           DR. CARSON: And then Mr. Merrill Goozner,  
12 who is our acting consumer representative, has a  
13 statement.

14           MR. GOOZNER: Thank you Dr. Carson.

15           While I do not have a conflict of interest,  
16 I would like to include a statement for the record.  
17 When I agreed to become a temporary member of this  
18 committee about two months ago, I did not know which  
19 company was involved. But when I opened the review  
20 material sent to me by the FDA less than two weeks  
21 ago, I learned that the company involved was Amgen.

22           I immediately informed the advisory

1 committee staff that I have written extensively about  
2 Amgen in the past decade in a book and on my own  
3 website, much of which could be considered critical.  
4 None of those writings involve this drug or this  
5 disease.

6 I told the FDA that some might perceive this  
7 as evidence of intellectual bias, but I thought I  
8 could provide objective advice representing consumers  
9 on this issue. The FDA took the matter under review  
10 and informed me yesterday that I could participate in  
11 the meeting.

12 DR. CARSON: Thank you.

13 Dr. George Benson will now introduce the  
14 issues that we are going to discuss today. Dr. Benson  
15 is the Deputy Director of the Division of Reproductive  
16 and Urologic Drugs.

17 DR. BENSON: We would also like to welcome  
18 you to this morning's advisory committee meeting for  
19 denosumab, and we particularly thank Dr. Carson and  
20 the members for agreeing to serve on this advisory  
21 committee.

22 This is the original biologic licensing

1 application for denosumab. Denosumab is a fully human  
2 IgG2 monoclonal antibody against receptor activator of  
3 nuclear factor kappa B or RANK ligand. RANK ligand  
4 stimulates its receptor, RANK, initiating  
5 intracellular signalling cascades, which promote  
6 osteoclast formation, differentiation, and activation,  
7 which leads to enhanced bone resorption and bone loss.

8 In the immune system, RANK ligand is  
9 involved in B cell and T cell differentiation, as well  
10 as maturation of antigen presenting or dendritic  
11 cells. Denosumab is dosed 60 milligrams every six  
12 months as a subcutaneous injection administered by a  
13 health care provider.

14 The new biologic licensing application seeks  
15 four separate indications for denosumab. These are  
16 treatment of postmenopausal osteoporosis, prevention  
17 of postmenopausal osteoporosis, treatment and  
18 prevention of bone loss in patients undergoing hormone  
19 ablation therapy for breast cancer, and therapy and  
20 prevention of bone loss in patients undergoing hormone  
21 ablation for prostate cancer.

22 The primary trial submitted to support

1 approval of the treatment of postmenopausal  
2 osteoporosis indication is an 8,000 patient fracture  
3 trial. The other three indications are supported by  
4 smaller studies, which use bone mineral density as the  
5 primary endpoint. Once an agent has demonstrated  
6 fracture reduction in one patient population, the  
7 division currently allows BMD to be used as the  
8 primary endpoint in studies of other patient  
9 populations.

10           The first two indications, treatment and  
11 prevention of postmenopausal osteoporosis, are being  
12 primarily reviewed by the Division of Reproductive and  
13 Urologic Products, and the two indications dealing  
14 with hormone ablation in cancer populations are being  
15 primarily reviewed by the Division of Biologic  
16 Oncology Products. Denosumab represents the first  
17 biologic product and the first monoclonal antibody to  
18 seek approval for any of these four indications.

19           Therapy seeking and indication for treatment  
20 of osteoporosis are required to demonstrate fracture  
21 efficacy. As previously stated, once fracture  
22 efficacy is established for a particular agent, BMD

1 can be used for evaluation of prevention of  
2 osteoporosis and for evaluation of efficacy in other  
3 populations or with new dosing regimens.

4 For comparative efficacy labeling claims  
5 between different agents, a head-to-head fracture  
6 trial is currently required. BMD findings alone  
7 cannot be extrapolated to predict differences in  
8 fracture efficacy.

9 Osteoporosis is defined as a systemic  
10 skeletal disorder of compromised bone strength,  
11 predisposing an individual to an increased risk of  
12 fracture. Currently, an estimated 10 million people  
13 in the United States have osteoporosis, 8 million  
14 women and 2 million men. An estimated 34 million  
15 people have low bone mass and are at risk for  
16 developing osteoporosis.

17 Currently there are 10 products available  
18 for the treatment of postmenopausal osteoporosis, five  
19 bisphosphonates, one SERM, one parathyroid hormone  
20 analog, and three calcitonin products. The majority  
21 of these agents also have the prevention of  
22 osteoporosis as an indication. These agents are dosed



1 daily to once yearly.

2 Prostate cancer is the most commonly  
3 diagnosed cancer in men and breast cancer is the most  
4 commonly diagnosed cancer in women. Reduction in sex  
5 steroid levels is a well recognized etiology of bone  
6 loss. No therapies are currently approved to treat  
7 bone loss associated with hormone ablation therapy.

8 Therapeutic monoclonal antibody products  
9 have been approved for various conditions, including  
10 cancers, organ rejection, and autoimmune disorders.  
11 Many have had serious safety issues identified both  
12 pre- and post-approval. Some have required medication  
13 guides, FDA alerts, or risk evaluation and mitigation  
14 strategies. A summary of the safety issues occurring  
15 with monoclonal antibodies can be found in Appendix A  
16 of the FDA briefing document.

17 The Food and Drug Administration Amendments  
18 Act of 2007 provides new authority to the FDA to  
19 require REMS. A REMS is a risk management plan that  
20 utilizes strategies that go beyond professional  
21 labeling to ensure the drug benefits outweigh risks.  
22 A REMS can include a medication guide for patients, a

1 communication plan for health care professionals, and  
2 elements to assure safe use.

3           The elements to ensure safe use is the most  
4 restrictive element that may be required as part of a  
5 REMS. These elements can include prescriber training  
6 or certification; drug administration limited to  
7 certain health care settings; or required monitoring  
8 of patients.

9           Review of the efficacy data shows that  
10 denosumab is effective in all four trials, which were  
11 submitted to support approval of all four indications.  
12 No head-to-head fracture studies, however, comparing  
13 denosumab with other agents have been performed.

14           The primary issues for consideration at  
15 today's advisory committee meeting involves safety  
16 issues, which have been identified during the review  
17 and include the occurrence of serious infections,  
18 development of new malignancies, dermatologic adverse  
19 events, and findings that suggest a potential for over  
20 suppression of bone remodeling.

21           With regard specifically to the two  
22 indications involving breast and prostate cancer

1 populations, there are further issues for  
2 consideration. A growing body of evidence suggests  
3 the promotion of tumor growth may exist for therapies  
4 in which there is no known direct relationship between  
5 the affected receptors and tumor proliferation.

6           Secondly, the impact of agents for  
7 supportive care of cancer patients should be carefully  
8 evaluated to identify any detrimental effects on  
9 cancer outcomes, such as progression free survival and  
10 overall survival.

11           We will ask the committee this afternoon to  
12 consider these safety concerns in the evaluation of  
13 the risk/benefit ratio for each of the four bone  
14 indications being sought for denosumab. Thank you.

15           DR. CARSON: Thank you very much. Let me  
16 now ask the sponsor to begin their presentation, and  
17 Dr. Paul Eisenberg is the senior vice-president and  
18 will direct his team through their presentation.

19           DR. EISENBERG: Good morning. Thank you  
20 Dr. Carson, members of the committee. My name is Paul  
21 Eisenberg. I'm responsible for Amgen's global  
22 regulatory and safety organizations.

1           First, on behalf of the many Amgen  
2 scientists who've worked to develop denosumab over the  
3 past 15 years into a therapy to prevent bone loss, we  
4 want to thank the committee today for your time and  
5 considering the data we will present. It's an  
6 extensive presentation this morning and we appreciate  
7 that it will take some time.

8           The clinical realization of the potential of  
9 denosumab as a specific inhibitor of RANK ligand as a  
10 therapeutic modality is a true example of bench-to-  
11 bedside research that translated the discovery of a  
12 key mechanism for regulating bone resorption into a  
13 novel therapeutic.

14           I'll be making some additional comments in  
15 regard to the specific clinical indications that FDA  
16 has highlighted that we're seeking. Following my  
17 introduction, Dr. Ethel Siris, who is an expert in  
18 osteoporosis, will speak briefly on clinical aspects  
19 relating to postmenopausal osteoporosis and bone loss  
20 that occurs in women and men treating with hormone  
21 ablative therapies, as well as the need for additional  
22 therapies.

1           Following Dr. Siris' presentation, Dr. David  
2   Lacey, the pathologist whose lab led the discovery of  
3   the RANK ligand pathway, will be commenting on the  
4   scientific basis supporting the use of denosumab  
5   clinically in the treatment and prevention of bone  
6   loss. He is also going to specifically review data  
7   that address concerns regarding the RANK pathway in  
8   immune responses and the malignancy.

9           These data are very informative with respect  
10   to the clinical context in terms of the data that  
11   we'll be presenting from our pivotal registration  
12   studies, which Dr. Stehman-Breen will present.

13           Finally, I'm going to conclude with Amgen's  
14   presentation of the ongoing clinical trials and  
15   planned studies that continue to support the safety  
16   profile of denosumab in these indications. In  
17   aggregate, the program we will be presenting this  
18   morning presents compelling evidence of efficacy  
19   supported by a comprehensive pharmacovigilance  
20   program.

21           Now as noted already, denosumab is a human  
22   monoclonal antibody that inhibits RANK ligand. By

1 inhibiting RANK ligand, it's binding to its receptor  
2 on the osteoclast, bone resorption is reduced.  
3 Dr. Lacey will be reviewing in greater detail the work  
4 of Amgen scientists in understanding this pathway.

5           As FDA has noted, denosumab has been studied  
6 in the treatment and prevention of postmenopausal  
7 osteoporosis and in bone loss that occurs in women and  
8 men treated with hormone ablative therapies that  
9 decrease sex hormone levels. The studies to support  
10 the use of denosumab in these indications were  
11 developed in collaboration with FDA based on draft  
12 guidance on the development of new therapies for the  
13 treatment of postmenopausal osteoporosis.

14           As already highlighted, the regulatory  
15 guideline highlights the need to validate that  
16 increases in bone mineral density attributable to a  
17 new therapeutic translate into fracture reduction as  
18 confirmation of increased bone strength induced by  
19 that therapeutic.

20           Amgen's pivotal registration study, the 216  
21 study, and we've provided you handout of each of the  
22 pivotal studies that we performed, included both the

1 fracture endpoint and the BMD assessment. For the  
2 prevention of postmenopausal osteoporosis and in the  
3 treatment and prevention of bone loss in women  
4 undergoing hormone ablation therapy, the BMD was the  
5 only endpoint in the studies that we performed, based  
6 on the validation of fracture reduction in the 216  
7 study. But in men with prostate cancer treated with  
8 ADT, Amgen pursued a more extensive program that  
9 included both bone mineral density assessment, as well  
10 as a prespecified fracture prevention endpoint.

11           The rationale for use of denosumab in the  
12 prevention of bone loss associated with hormone  
13 ablation therapies was the recognition that  
14 osteoporotic fractures in these patients have been  
15 associated with poor outcomes independent of the  
16 success of treatment of the underlying malignancy.

17           I'll now ask Dr. Siris to comment briefly on  
18 the clinical context for the conditions we will be  
19 discussing this morning. Thank you.

20           DR. SIRIS: Thank you very much, and good  
21 morning ladies and gentleman. My name is Ethel Siris.  
22 I'm an osteoporosis specialist at the Columbia

1 University Medical Center, New York Presbyterian  
2 Hospital in New York City, and I'm the immediate past  
3 president of the National Osteoporosis Foundation.  
4 I'd like to state for the record that my comments this  
5 morning are coming from me and I'm not representing  
6 any of those organizations in what I have to say to  
7 you today.

8           Let me start by coming back to what  
9 Dr. Benson said a few minutes ago. Osteoporosis is  
10 defined as a skeletal disorder that is compromised by  
11 reduced bone strength, which predisposes individuals  
12 to an increased risk of fracture. Fracture is the  
13 complication of having this reduced bone strength.  
14 And bone strength is really a function in part of the  
15 amount of bone, the quantity, which is something we  
16 can estimate when we do a bone density test.

17           But the reduced bone strength is also a  
18 function of the quality of bone. And with bone loss,  
19 there is a change in bone microarchitecture such that  
20 bone is less well put together and therefore becomes  
21 weaker. And you can appreciate this interconnected  
22 set of cylinders and plates in normal and here you



1 have these attenuated struts, this one's broken and  
2 this one is in the process of separating, and that  
3 causes a loss of bone strength.

4 Now the United States Surgeon General's  
5 report in 2004 highlighted that this is a serious  
6 public health problem. Indeed there are, as you  
7 heard, 10 million Americans with osteoporosis, another  
8 34 million with low bone mass, which is a precursor to  
9 osteoporosis, but more importantly is a risk factor  
10 itself. Some people with low bone mass are actually  
11 at significant risk.

12 One in two women over the age of 50 will  
13 have a fracture in their remaining lifetimes. There  
14 indeed were 2 million fractures in the year 2005, of  
15 which 29 percent occurred in men, the remainder in  
16 women.

17 Fractures are associated with significantly  
18 negative impacts on the quality of life, and in case  
19 of hip fracture, and to some degree vertebral  
20 fracture; there is an increase in mortality in the  
21 post-fracture period. As you see from the pie chart,  
22 about 27 percent of fractures are spine fractures,

1 14 percent occur at the hip, 19 percent at the wrist,  
2 about 7 percent are pelvic fractures, and another  
3 third of fractures are at a variety of other skeletal  
4 sites. Once you've had one fracture you're at high-  
5 risk of more.

6           There are subsets of individuals who are at  
7 a different level of risk and those are individuals  
8 who are receiving hormone ablation therapy. Hormone  
9 ablation therapy for both breast and prostate cancer  
10 is a mainstay therapy for estrogen receptive positive  
11 breast cancer and for men with prostate cancer. And  
12 indeed, we believe that the number of patients with  
13 nonmetastatic cancers undergoing hormone ablation in  
14 the United States today includes between 300,000 and  
15 450,000 women with breast cancer who receive aromatase  
16 inhibitors and another 140,000 men with prostate  
17 cancer undergoing androgen deprivation therapy. These  
18 therapies are helping these people to live longer and  
19 function better and they are important treatments for  
20 them.

21           Unfortunately, one of the consequences of  
22 hormone ablation is bone loss, and this bone loss is

1 associated with an increased risk for fracture, and  
2 depending on which study you look at, its anywhere  
3 from an 11 to a 53 percent relative risk of having  
4 fractures; and this is a subpopulation that needs to  
5 be helped.

6           Now today we look at the diagnosis of  
7 osteoporosis based on measurement of bone mineral  
8 density and we use something called a T-score. A  
9 T-score, as you see at the bottom, in a postmenopausal  
10 patient, represents the number of standard deviations  
11 above or below the mean value of bone density in a  
12 reference population of healthy young women.

13           So it's been stated by the World Health  
14 Organization that if you have a T-score that is better  
15 than minus 1, you're normal. If you're between  
16 minus 1 and minus 2.5, you have low bone mass,  
17 sometimes called osteopenia, and if you have a T-score  
18 of minus 2.5 or below, that's osteoporosis. And while  
19 this is a very useful way of helping us categorize  
20 people, and indeed diagnosis is based upon T-scores,  
21 it turns out this is not the best way to assess who is  
22 at increased risk. You have to go beyond T-score to

1     determine who is at increased risk for fracture.

2                 Now this slide shows data from a study  
3     called the National Osteoporosis Risk Assessment, or  
4     NORA, which enrolled 200,000 U.S. women, all  
5     postmenopausal between 50 and 99, who did not have a  
6     diagnosis of osteoporosis and were not receiving  
7     treatment for osteoporosis. And at baseline, as shown  
8     on the X axis, their bone mineral density values  
9     ranged all the way from plus one down to minus 3.5.

10                At one year post-baseline, data were  
11    collected on fractures in that first post-baseline  
12    year, and you can see that the fracture rates were the  
13    highest in the people with the lowest bone mineral  
14    density measurements. And that's the whole point of  
15    doing a bone density.

16                If you look at the population distribution  
17    in NORA, shown under this bell shaped curve, you see  
18    that the majority of women range from normal down to  
19    osteopenic, and that's because there are more people  
20    who have an osteopenic T-score than have an  
21    osteoporotic T-score in our country. And if we then  
22    looked at the actual number of women who fractured,

1 shown in the yellow bars, it turns out that 52 percent  
2 of the people who fractured had osteopenia and that's  
3 simply because, although they may have been at  
4 somewhat more moderate risk, there are so many more of  
5 them, that if you simply think about treating people  
6 with osteoporosis, you will miss a great number of  
7 people with osteopenia who actually are having the  
8 fractures.

9           And what this tells you is not that you must  
10 treat all people with osteopenia. No, it says you  
11 must risk stratify people with osteopenia, because  
12 some are at low-risk and some are at high-risk and you  
13 don't want to miss the people at high-risk, you want  
14 to treat those, so the people at low-risk can be  
15 reassured and re-evaluated over time.

16           The way to do this is with a new tool from  
17 the World Health Organization called FRAX. FRAX is a  
18 tool that helps you calculate the 10 year absolute  
19 probability of hip fracture and a group of fractures  
20 called major osteoporotic fractures, spine, hip,  
21 forearm, and humerus, by taking into account not only  
22 the bone density at the hip, but adding to it a series

1 of validated clinical risk factors, which have been  
2 shown to be effective at better predicting who's at  
3 risk for fracture. And it basically allows the  
4 clinician to make a treatment decision based on  
5 absolute fracture risk. Now it's most useful in the  
6 patient with osteopenia.

7           Here's an example of how you use FRAX in a  
8 U.S. woman who is 67 years of age. She has a previous  
9 fracture. Her mother also broke a hip; these are two  
10 important risk factors. And very significantly, her  
11 T-score is minus 2.1. She is osteopenic. But because  
12 of her age, 67, and her risk factors that are  
13 positive, her 10 year probability of a major fracture  
14 is 36 percent and her 10 year probability for a hip  
15 fracture is 4.7 percent.

16           How do we use that information?

17           Well the National Osteoporosis Foundation  
18 guide recommends that postmenopausal women and men  
19 over the age of 50 presenting with the following, any  
20 one of the following, should be considered for  
21 treatment. Anyone who has a hip or a vertebral  
22 fracture essentially has osteoporosis and should be

1 treated. Anyone with a T-score of minus 2.5 or below  
2 at the hip or the spine has osteoporosis, and this is  
3 someone who would fit into the treatment indication  
4 for osteoporosis.

5 But the third category, or those individuals  
6 with low bone mass and, by FRAX, a 10 year probability  
7 of fracture, the T-scores between minus 1 and minus  
8 2.5 at the hip or spine, and they either have a  
9 10-year probability of hip fracture of 3 percent or  
10 greater, the case I showed you was 4.6 percent, or a  
11 10-year probability of major fractures equal to or  
12 greater than 20 percent. The patient I showed you had  
13 a risk of 36 percent.

14 So this is an individual who would fall  
15 under the prevention indication, because this is  
16 somebody who doesn't have osteoporosis, but who is at  
17 high-risk for fracture, and therefore we would  
18 recommend the patient be treated. And by the way,  
19 clinical judgment is also a big part of these  
20 decisions. FRAX helps clinical judgment.

21 Now, as was noted, we are fortunate to have  
22 a series of therapies available for our patients and

1 we are grateful to have them, but I think it's  
2 critical to point out that one size does not fit all  
3 in postmenopausal women with low bone mass or  
4 osteoporosis.

5           With the oral bisphosphonates, there may  
6 well be GI intolerance. Tolerance is a big part of  
7 it. Patients won't take the drug if it upsets their  
8 stomachs or if it's contraindicated. Clearly, there  
9 are side effects for every one of these therapies.  
10 They all have side effects, which in some instances  
11 prevent you from using the drug, and in other  
12 instances the patient is afraid of the side effects  
13 and won't take the drug.

14           There are different efficacy profiles. Some  
15 of these drugs are indicated for the prevention of  
16 vertebral fracture, some for vertebral and non-  
17 vertebral, some for vertebral and hip, some for all  
18 three. They vary, but there are different efficacy  
19 profiles.

20           Finally, there are renal issues with  
21 bisphosphonates, and especially IV bisphosphonates;  
22 you really have to be very careful using these agents



1 in people with poor renal function.

2           Very importantly, we have no approved  
3 therapies for bone loss in breast and prostate cancer  
4 patients who are on hormone ablation therapy. We see  
5 these people in the office, we know that they are  
6 losing bone, and we don't have an approved treatment  
7 for them.

8           And finally, I would say that one of the  
9 biggest problems in our field today is adherence. It  
10 turns out that about half of patients put on an oral  
11 agent for osteoporosis are not taking it at the end of  
12 one year. We therefore want to have treatments that  
13 patients will actually take. A twice yearly injection  
14 in a primary care doctor's office may offer a  
15 considerable convenience for the patient and also  
16 allows the doctor to know whether or not the patient  
17 is actually receiving that therapy.

18           I cannot underscore enough how important it  
19 is for us to do a better job getting patients to take  
20 the treatments we recommend, because if you don't take  
21 it, it turns out it doesn't work and you are therefore  
22 subjected to the cost, the potential for side effect

1 without the benefits, so adherence is a critical  
2 issue.

3           Let me say in conclusion that this is a  
4 serious public health problem; it affects a great many  
5 people. We are getting better at identifying those  
6 who are at risk. We need to have a broad range of  
7 options so that we truly can tailor therapy to the  
8 patient and I think that we have to do a better job,  
9 because this is a costly and serious issue that we  
10 really have to change in our country.

11           Thank you very much for your attention. I  
12 will turn the podium over to Dr. Lacey.

13           DR. LACEY: Good morning. Thank you  
14 Dr. Siris.

15           As Dr. Siris, I think has compellingly  
16 reviewed, there is, I think, an important need for  
17 another option for the treatment of osteoporosis. And  
18 what I want to do in this next section is to briefly  
19 review the history of the science at Amgen and the  
20 therapeutic that we're presenting today, denosumab,  
21 which we feel represents a novel and targeted approach  
22 to the regulation of bone loss.

1           So this is a historic slide. Just looking  
2   at this slide takes me back about 15 years ago. Amgen  
3   was in the midst of a gene discovery program called  
4   the Amgen Genome Program, and in that program, we were  
5   trying to determine the function of novel genes with  
6   the hope that we would find one that would lead to an  
7   important new therapy.

8           One of the first genes that we've identified  
9   that we wanted to determine its function, was a gene  
10  called osteoprotegerin. The name wasn't  
11  osteoprotegerin at the time, but it quickly was named  
12  that after some of our observations.

13          So the two radiographs that you see on this  
14  slide are the results of the first experiment, and the  
15  way Amgen determined the function was to make animals  
16  that overexpressed different gene products. In this  
17  case the gene product was osteoprotegerin. And you  
18  can clearly see, and it was an amazing thing for me to  
19  see the first time I saw this radiograph, that the  
20  bones on the right side are very radiodense compared  
21  to the bones on the left, normal shape, radiodense.

22          Now as an academic pathologist who had

1 recently come to Amgen with a background in bone cell  
2 biology, specifically in osteoclast biology, this was  
3 a very exciting finding. And so when you think about  
4 it, it could be either an osteoblast defect, or an  
5 osteoclast defect, we rapidly determined in histologic  
6 sections that it was in fact a deficiency in the  
7 number of osteoclast that typified this finding. So  
8 what we quickly did was make recombinant OPG and put  
9 it in tissue culture systems looking for the capacity  
10 to blunt osteoclast formation, and, in fact, that was  
11 the mechanism.

12           Now it's been stated before, osteoprotegerin  
13 is a member of the tumor necrosis factor receptor  
14 superfamily. Superfamily designations, just for those  
15 of you who may not know, is a structural relatedness;  
16 in other words, protein structure analyzed by  
17 analytical methods and we align things into families.  
18 The tumor necrosis factor receptor superfamily has  
19 been very adaptable. It has functions outside of  
20 immunity including in vasculature, the nervous system,  
21 skin adnexal formation, and in the basis of this  
22 observation here, in bone metabolism.

1           So using OPG, which is a secreted decoy  
2   receptor based on its sequence, we rapidly determined  
3   that it bound to a new family member, RANK ligand, and  
4   then that implicated RANK as a cellular receptor.

5           So how do these things function together in  
6   the bone microenvironment?

7           This is going to be a build slide; you have  
8   probably the last slide in your handout. Bone mass is  
9   determined by the interplay of osteoblast that make  
10   bone, osteoclast that resorb bone. Through a series  
11   of many studies conducted by Amgen and others, the  
12   osteoblast governs this process and responds to  
13   systemic factors, including cytokines, growth factors,  
14   and hormones. It releases in this figure here. The  
15   green either coffee bean or football shaped figures is  
16   RANK ligand. It engages the cellular receptor on the  
17   surface of osteoclast and their precursors, and it  
18   drives an intricate cellular cascade.

19           Our pathway, or our route, ended this  
20   discovery process via the discovery of osteoprotegerin  
21   or OPG. It is a secreted decoy receptor. It's also  
22   secreted by the osteoblast. And so the osteoclast can

1    govern in the bone microenvironment activities that  
2    support bone resorption through the production of RANK  
3    ligand and activities that dampen that process through  
4    the production of OPG.

5                Now, with the knowledge of the family, now,  
6    further studies were performed with RANK and RANK  
7    ligand, and animals were constructed by deleting those  
8    genes. And the way those genes were deleted, they  
9    were absent from the time of conception, and so the  
10   findings that were revealed in these experiments  
11   reflected an impact not only of what would happen in  
12   an adult, but also reflects things that occur during  
13   embryogenesis and during fetal development.

14              So what did we learn from these experiments?  
15   What we learned and confirmed is that, in fact, this  
16   pathway is seminal in its importance for osteoclast  
17   formation, function, and survival. Secondly, in the  
18   developing embryo, these factors are required for  
19   lymph node formation. And an interesting finding is  
20   that in adult females, during gestation, this pathway  
21   is essential for the proliferative step that occurs in  
22   the breast prior to lactation, and so the functions of

1     this pathway are varied.

2                 That last finding was one of the  
3     underpinnings that we have taken forward and applied  
4     to our discovery program around the utility of RANK  
5     ligand inhibition in oncology.

6                 Now, reflecting on the fact that there was  
7     an impact on lymph node formation in the knockout  
8     animals, or the gene ablated animals, and the fact  
9     that RANK and RANK ligand molecules are expressed on  
10    immune cells, we of course, were interested in  
11    potential immune activities of RANK ligand inhibition.  
12    And I crossed a broad set of experiments here  
13    numbering 27 different studies. We've studied RANK  
14    ligand inhibition and the basal immune profile,  
15    responses to immune challenges, responses to  
16    infectious challenges, and autoimmune inflammation  
17    models, and find that there is no evidence for  
18    immunosuppression.

19                Now, there were two reasons why we're  
20    interested in oncology. Firstly, we knew that the  
21    osteoclast was a key cell involved in the bone  
22    destructive process that accompanies the malignant

1 process of tumors in bone. The second discovery,  
2 which was the mammary proliferation and the lactation,  
3 was the second reason to be involved in cancer. We  
4 performed 13 different studies, and we've looked at  
5 the impact of RANK ligand inhibition on skeletal tumor  
6 progression, the capacity for tumors to metastasize to  
7 bone, and found in those cases that RANK ligand  
8 inhibition actually suppresses those processes and  
9 leads to increased survival.

10 In mammary tumorigenesis models exploring  
11 the combined effect of carcinogen and hormone  
12 treatments, RANK ligand inhibition suppresses that  
13 process. Importantly, a RANK ligand inhibition does  
14 not impact tumors that lie outside of the skeleton, so  
15 subcutaneous tumors there is no effect of RANK ligand  
16 inhibition. And probably most importantly, the use of  
17 RANK ligand inhibition did not interfere with  
18 antitumor therapies, and the ones that we've explored  
19 include chemotherapy, targeted therapy, and hormonal  
20 therapy.

21 So with that as a background, what I want to  
22 discuss in the next several slides is the approach



1     that Amgen took to identify a novel therapeutic  
2     targeting the RANK of RANK ligand pathways. We wanted  
3     to find the optimal RANK ligand inhibitor. And to do  
4     that, I think that turning back to the model here, we  
5     thought that an optimal RANK ligand inhibitor could be  
6     patterned after OPG. OPG is very potent. We also  
7     wanted a therapy that was selective. And we would  
8     like to have a therapy, if possible, that would afford  
9     a favorable pharmacodynamic profile that would lead to  
10    infrequent dosing intervals, which would be of  
11    benefit, particularly in the area of postmenopausal  
12    osteoporosis.

13                So in factoring all those things together  
14    and realizing that this was not going to be a pathway  
15    of minimal-to-small molecule interdiction, monoclonal  
16    antibodies seem to be the ideal approach to this  
17    particular therapeutic opportunity.

18                So with this as a realization, Amgen  
19    scientists then went on a hunt to find the optimal  
20    monoclonal antibody. The result of that process is  
21    denosumab. It's named denosumab. And what it is, is  
22    a human IgG2 monoclonal antibody. This IgG2 antibody

1 is identical to all the other circulating IgG2  
2 antibodies that circulate in your body with the  
3 important difference is its antigen recognition domain  
4 recognizes human RANK ligand.

5           The molecule is very potent, 3 peak molar  
6 affinity, which should allow for low doses. It is  
7 selective against other family members, against other  
8 TNF family members. And importantly, it does not  
9 recognize rodent RANK ligand, which has precluded our  
10 ability to do carcinogenicity studies, and it has a  
11 suitable half-life amenable to infrequent dosing  
12 intervals. So based on what we were looking for,  
13 denosumab was an ideal therapeutic.

14           So here's how it works. This is, again, a  
15 picture of that cartoon again. Denosumab binds to  
16 RANK ligand, prevents its association with osteoclast  
17 and their precursors. And as a result, bone  
18 resorption is suppressed as a result of an effect on  
19 osteoclast pathway.

20           So preclinically, we've looked at the  
21 effects of denosumab in a nonhuman primate model of  
22 postmenopausal osteoporosis or hormone ablation, and

1 this is the OVX primate model. And the results of the  
2 experiment were shown in this slide with bone mineral  
3 density on the left, bone strength on the right.

4 I'll just quickly step through the findings.  
5 In the OVX animals alone, over a six month period,  
6 they dropped their bone mineral density by about  
7 5 percent to 6 percent. Denosumab treated OVX animals  
8 increased their bone mass by that same amount. But  
9 within three months, that increase with denosumab  
10 continues out to 16 months, where there is a  
11 difference between baseline of 11 percent and a  
12 difference between the OVX and denosumab group and the  
13 OVX alone, being approximately 16 percent.

14 Perhaps the most exciting result on this  
15 slide is the bar graph on the right, and that's  
16 looking at the effect of this treatment on bone  
17 strength. And what's unusual about this result is the  
18 denosumab treated animals not only have strength  
19 that's above the OVX control, but also above the sham.  
20 So this implication is this increase in bone mass has  
21 led to bones that are very strong.

22 So in summary, denosumab is a potent

1 selective RANK ligand inhibitor that suppresses  
2 osteoclast formation, function, and survival.  
3 Denosumab could not be used in the traditional rodent  
4 carcinogenicity studies and that's according to  
5 guidelines.

6           In safety studies, nonhuman primates were  
7 exposed to denosumab, but up to 150 fold to human  
8 exposure for 12 months. And the only findings that  
9 were found were those that you would expect in bone.  
10 And lastly, denosumab increased bone mass and strength  
11 in ovariectomized nonhuman primates in a 16 month  
12 study, the one I just showed you.

13           So in conclusion we think that denosumab  
14 represents an ideal therapy targeted at a key  
15 regulator for osteoclast formation activation and  
16 survival.

17           Now I'd like to introduce Catherine Stehman-  
18 Breen who will go over the efficacy and safety results  
19 from our clinical trials. Thank you.

20           DR. STEHMAN-BREEN: Good morning. My name  
21 is Catherine Stehman-Breen and I'm the bone  
22 therapeutic area head at Amgen. Now you've heard from

1 Dr. Siris about the public health impact of bone loss,  
2 both due to age and to hormone ablation therapy and  
3 the need for innovative new therapies. You've just  
4 heard from Dr. Lacey about the exciting preclinical  
5 discoveries 15 years ago that have formed the basis of  
6 the denosumab clinical program and the targeted  
7 mechanism of action of denosumab that uses the body's  
8 own natural mechanisms to regulate bone turnover.

9 I'm going to spend my portion of the  
10 presentation highlighting how these preclinical  
11 discoveries have translated into remarkable efficacy  
12 and a favorable safety profile. Now the denosumab  
13 clinical program is a large program. There were 30  
14 studies included as part of the biologic license  
15 application. I'm going to focus my presentation on  
16 the four pivotal studies that are highlighted here.

17 I'll begin my presentation by summarizing  
18 the efficacy data from the studies in the treatment  
19 and prevention of bone loss. I'll follow that by  
20 summarizing the efficacy data from the two studies in  
21 the treatment and prevention of bone loss due to  
22 hormone ablation therapy. And then I'll conclude my

1 presentation by summarizing the aggregate safety data  
2 from these four studies.

3 I'm going to start with the clinical  
4 efficacy evaluation in the treatment and prevention of  
5 postmenopausal osteoporosis. This data will  
6 demonstrate significant reductions in bone resorption  
7 that translate into robust increases in bone mineral  
8 density and importantly reductions in fracture risk.

9 Now this slide summarizes the study design  
10 for our PMO fracture study. This study was conducted  
11 to determine whether denosumab administered at 60  
12 milligrams subcutaneously every six months, the same  
13 dose that was used in all of our bone loss clinical  
14 trials, would reduce the incidence of new vertebral  
15 fracture, in addition to two key secondary endpoints,  
16 non-vertebral fracture and hip fracture. New  
17 vertebral fracture was identified morphometrically by  
18 accessing reductions in vertebral height. All of our  
19 fractures were confirmed using an external central  
20 reader.

21 The women that were included in this study  
22 were required to have osteoporosis with T-scores that

1 were between negative 2.5 and negative 4 at either the  
2 lumbar spine or the total hip. Because this was a  
3 placebo controlled study, women were not allowed to  
4 enroll if they had any severe or more than two  
5 moderate vertebral fractures. It is also important to  
6 note that this study didn't exclude women on the basis  
7 of renal function. And as Dr. Siris pointed out, this  
8 is an area of unmet medical need.

9           Seventy-eight hundred and eight women were  
10 randomized to either receive denosumab or a placebo.  
11 They were followed for 36 months, and during that  
12 period they received calcium and Vitamin D as all  
13 subjects did in our clinical trials.

14           Now this study had an important component to  
15 it and that's an open-label 2 study. Forty-five  
16 hundred and fifty women were enrolled in this long-  
17 term extension study, where they will be followed for  
18 an additional seven years, and this will provide  
19 important long-term safety data in this population.

20           Now these are the baseline characteristics  
21 of the population that we studied; 82 percent of the  
22 women in the placebo group and 84 percent in the women

1 that received denosumab completed the study. The mean  
2 age of the women was 72 years, and as you can see,  
3 most of the women qualified based on their lumbar  
4 spine bone mineral density. The prevalence of  
5 vertebral fracture at baseline was 23.4 percent in  
6 women receiving placebo and 23.8 in those women  
7 receiving denosumab.

8           Now administration of denosumab resulted in  
9 rapid and sustained reductions in bone turnover as  
10 reflected here by reductions in serum C-telopeptide,  
11 or CTX, which is a collagen breakdown product. Serum  
12 levels of CTX over the course of the study are  
13 illustrated in yellow and time is on the horizontal  
14 axis, while percent change from baseline is on the  
15 vertical axis. As you can see, after administration  
16 of denosumab, there is a rapid 86 percent reduction in  
17 CTX by month 1. Over the remainder of the six month  
18 dosing interval, there is a slight attenuation in the  
19 reduction of CTX with an 86 percent reduction at the  
20 pre-dose time point at month 6.

21           Now if you will focus on month 6, 12, 24,  
22 and 36, these are the pre-dose time points. And as



1   you can see, the level of reduction in CTX is  
2   generally maintained over that period with a  
3   72 percent reduction at the 36 month pre-dosing  
4   interval. And it is also interesting to note that  
5   100 percent of subjects had reductions in CTX after  
6   the first dose of denosumab.

7               Now these reductions in bone turnover  
8   translated directly into increases in bone mineral  
9   density. The difference in the mean lumbar spine bone  
10  mineral density was 9.2 percent at 36 months and  
11  6 percent at 36 months at the total hip. These  
12  increases in bone mineral density were maintained over  
13  the course of the study and, although not shown here,  
14  have been maintained over six years in our Phase 2  
15  study.

16              Now the PMO study successfully met its  
17  primary endpoint, demonstrating significant reductions  
18  in the incidence of new vertebral fracture. Denosumab  
19  reduced the risk of new vertebral fracture at one,  
20  two, and three years. At three years, the subject  
21  incidence of new vertebral fracture in the placebo  
22  group was 7.2 percent and 2.3 percent in the denosumab

1 group, resulting in a 68 percent reduction in the risk  
2 of new vertebral fracture. Risk reduction was  
3 consistent over time and was seen as early as one  
4 year. It did not vary across a wide variety of  
5 patient characteristics, including renal function.

6 Now this study also met its key secondary  
7 endpoint, demonstrating a significant reduction in the  
8 risk of hip fracture. As you can see in this figure,  
9 there was a 40 percent reduction in the risk of hip  
10 fracture at 36 months. This reduction was seen early  
11 as you can see by the early separation of the Kaplan-  
12 Meier curve.

13 This study also met its other secondary  
14 endpoint, demonstrating reduction in the risk of non-  
15 vertebral fracture. As you can see, at 36 months  
16 there was a 20 percent reduction in the risk of non-  
17 vertebral fracture. As you heard from Dr. Siris,  
18 these types of fractures, which include wrist,  
19 humerus, hip, and a variety of other osteoporotic  
20 related fractures, are an important source of  
21 morbidity and mortality in this patient population.

22 Now I've summarized the key efficacy data

1 from the study, but this study also had another key  
2 component to it, and that was the bone biopsy study.  
3 And I'd like to summarize some of the results of that  
4 substudy.

5           Now the primary reason to do a bone biopsy  
6 when assessing a new therapeutic is to ensure that the  
7 bone histology has not been altered in a negative way  
8 by that therapeutic, and this was demonstrated in a  
9 comprehensive evaluation of 241 biopsies that were  
10 obtained at baseline, 12, 24, and 36 months in three  
11 different studies. These biopsies were obtained at  
12 the iliac crest.

13           A bone biopsy from a denosumab treated  
14 subject, a representative biopsy that was obtained at  
15 12 and 24 months is illustrated on the left side of  
16 the slide. It demonstrates normal lamellar bone with  
17 no evidence of any abnormalities that you might be  
18 concerned about, such as marrow fibrosis,  
19 osteomalacia, or woven bone.

20           Measurements of bone remodeling using these  
21 biopsy specimens, which is termed histomorphometry,  
22 demonstrated findings that were also consistent with

1 reductions in bone turnover. Using one of these  
2 assessments that's called tetracycline labeling, we  
3 observed that about a third of the subjects didn't  
4 demonstrate any tetracycline labeling in either the  
5 cortical or trabecular bone. This is consistent with  
6 the mechanism of action of denosumab and also the  
7 level of reduction in bone turnover that we observed  
8 with the serum marker CTX.

9           Now we recognize that this level of  
10 suppression has generated some concern, but it's  
11 important to keep in mind that it's this level of  
12 suppression that has also resulted in increased bone  
13 strength in our preclinical models, increases in bone  
14 mineral density and reductions in fracture risk in our  
15 clinical studies. But as you will see when I  
16 summarize the safety data, it has also not been  
17 associated with any adverse consequences that one  
18 might be concerned about with reductions in bone  
19 turnover, such as atypical fractures, abnormalities in  
20 fracture healing, or osteonecrosis of the jaw.

21           Now we recognize that this study is a three  
22 year study, but as you'll hear later on in the

1 presentation, we will continue to monitor for this  
2 over the long-term.

3           Now let's turn and highlight the study  
4 design from our prevention of osteoporosis study. As  
5 Dr. Siris pointed out, there are many women who don't  
6 have osteoporosis who are at high-risk of fracture.  
7 And as she pointed out, this is due to a wide variety  
8 of well characterized risk factors. The PMO  
9 prevention study was conducted to determine whether  
10 denosumab would result in greater increases in lumbar  
11 spine bone mineral density at 24 months.

12           Women who were enrolled in the study were  
13 required to have lumbar spine T-scores that were in  
14 the osteopenic range between negative 1 and negative  
15 2.5. Three hundred and thirty-two women were  
16 randomized to either receive denosumab or a placebo  
17 and were followed for 24 months.

18           Now this study also had an important safety  
19 follow-up study, and that was a 24 month follow-up  
20 period that was designed to assess the effects of  
21 discontinuation of denosumab on both serum CTX and on  
22 bone mineral density. I'm gonna begin by summarizing

1 the efficacy data and then I'll follow that by  
2 describing the off treatment data.

3 Now this slide describes the baseline  
4 characteristics of the population. As you can see,  
5 87 percent of the subjects completed the study in the  
6 placebo group and 86 percent in the denosumab. As  
7 expected, the mean age was younger than in our PMO  
8 fracture study and most of the women qualified for the  
9 study based on their lumbar spine bone mineral  
10 density.

11 Now the difference in the mean bone mineral  
12 density was 7 percent at the lumbar spine and  
13 4.5 percent at the total hip. As you can see, these  
14 increases in bone mineral density were maintained over  
15 the course of the study and are quite similar to that  
16 that was observed our postmenopausal osteoporosis  
17 fracture study.

18 Now as I said, there was an off-treatment  
19 period after the initial 24 months of the study. The  
20 reversibility of denosumab is reflected by serum CTX,  
21 illustrated here by the yellow line, with time on the  
22 horizontal axis and serum CTX values on the vertical

1 axis. After discontinuation of denosumab, osteoclast  
2 function returns, bone turnover markers increased  
3 transiently above baseline, and then subsequently  
4 decreased back to near baseline levels. It is  
5 important to note that this pattern is consistent with  
6 other reversible antiresorptives, such as estrogen and  
7 raloxifene.

8           Now these CTX values directly translate into  
9 what we observed with regard to bone mineral density.  
10 Again, following the discontinuation of denosumab,  
11 osteoclast function returns, bone is resorbed, bone  
12 mineral density declines, and at 48 months remains  
13 1.8 percent above that observed in the placebo. These  
14 data suggest that denosumab treatment arrests the bone  
15 loss that would normally have occurred without  
16 treatment.

17           Now I finished summarizing the clinical  
18 efficacy data from the treatment and prevention of  
19 osteoporosis. These data have demonstrated  
20 significant and rapid reductions in bone resorption  
21 that have translated into robust increases in bone  
22 mineral density, and most importantly have

1 demonstrated significant reductions in fracture risk  
2 at the spine, at the hip, and at the non-vertebral  
3 sites.

4 I'm going to turn now and highlight data  
5 from our hormone ablation therapy studies. As you  
6 heard from both Dr. Eisenberg and Dr. Siris, there are  
7 no approved therapies for this indication, which is  
8 due to hormone ablation therapy, critical therapies in  
9 these patients. It is important to remember that  
10 women with breast cancer that are receiving androgen  
11 deprivation therapy have profound estrogen deficiency.  
12 It is the result of both their aromatase inhibitors,  
13 but also as the result of menopause.

14 You will see from these studies that  
15 denosumab results in increases bone mineral density,  
16 and importantly in men with prostate cancer receiving  
17 androgen deprivation therapy, reductions in vertebral  
18 fracture risk.

19 The HALT breast cancer study was designed to  
20 confirm that women with bone loss that is the result  
21 of estrogen deficiency, due to aromatase inhibitors,  
22 would have similar bone mineral density increases as



1 women with bone loss due to estrogen deficiency that  
2 is the result of aging. As you can see, the study  
3 design is almost identical to our PMO prevention  
4 study.

5           The HALT breast cancer study was conducted  
6 to determine whether denosumab would result in greater  
7 increases in lumbar spine bone mineral density than  
8 placebo at 12 months. Similar to the prevention  
9 study, women who enrolled in the study were required  
10 to have bone mineral densities that were in what's  
11 termed the osteopenic range or between negative 1 and  
12 negative 2.5. The women were required to have  
13 nonmetastatic disease, and as a reminder, all of these  
14 women were postmenopausal. Two hundred and fifty-two  
15 women were randomized to either receive denosumab or  
16 placebo and followed for 24 months.

17           The baseline characteristics of this  
18 population are highlighted here; 79 percent of the  
19 women in the placebo group and 83 percent of the women  
20 in the denosumab group completed the study. The mean  
21 age of the population is very similar to what was  
22 observed in our PMO prevention study. And, again,

1 most of the women qualified for the study based on  
2 their lumbar spine bone mineral density.

3           This study met its primary endpoint  
4 demonstrating significant increases in lumbar spine  
5 bone mineral density. The difference in the mean bone  
6 mineral density was 7.6 percent at the lumbar spine  
7 and 4.7 percent at the total hip. Now these figures  
8 may look familiar to you as the increases in bone  
9 mineral density are almost identical to that that we  
10 saw in our prevention study.

11           Now the HALT prostate cancer study was  
12 conducted to determine whether denosumab would result  
13 in greater increases in lumbar spine bone mineral  
14 density than placebo at 24 months in men with prostate  
15 cancer receiving androgen deprivation therapy. Men  
16 enrolled in the study had nonmetastatic prostate  
17 cancer and required to be either more than 70 years of  
18 age, or if they were less than 70 years of age, they  
19 had to have a history of osteoporotic fracture or a  
20 T-score of less than negative 1 at the lumbar spine,  
21 total hip, or femoral neck; 468 men were randomized to  
22 either received denosumab or placebo and were followed

1 for 36 months.

2           Seventy-seven percent of the men in the  
3 placebo group and 80 percent of the men in the  
4 denosumab group completed the initial 24 months of the  
5 study. At 24 months, the study was extended for an  
6 additional 12 months, and upon consent, as expected,  
7 there was some dropout resulting in 61 percent of the  
8 subjects in the placebo group and 64 percent of the  
9 subjects in the denosumab group completing the study.  
10 The mean age was 75 years and the prevalence of  
11 vertebral fracture was 23.7 percent in the placebo  
12 group and 21.1 percent in the denosumab group.

13           This study met its primary endpoint,  
14 demonstrating significant increases in lumbar spine  
15 bone mineral density. The difference in the mean bone  
16 mineral density was 7.9 percent at the lumbar spine  
17 and 5.7 percent at the total hip. These increases  
18 were maintained over the 36 months of the study.

19           Now importantly, this study also met its key  
20 secondary endpoint, demonstrating significant  
21 reductions in the incidents of new vertebral fracture.  
22 At 36 months, there was a 62 percent reduction in the

1 incidence of new vertebral fracture.

2           Now before I turn and begin to describe the  
3 safety data, I think it's important to point out the  
4 consistency of the data that we've seen across a wide  
5 variety of populations.

6           This study shows the percent change from  
7 baseline in either lumbar spine bone mineral density  
8 or hip bone mineral density at two years in each of  
9 the populations studied, and illustrates the  
10 remarkable consistency of bone mineral density gains.

11           But perhaps more striking is the consistency  
12 of fracture risk reduction that's illustrated here,  
13 the magnitude of the reduction in fracture risk in  
14 women with postmenopausal osteoporosis was 68 percent,  
15 and in men with prostate cancer receiving androgen  
16 deprivation therapy was 62 percent.

17           Because the mechanism of action of denosumab  
18 is targeted using the body's own natural mechanism to  
19 regulate bone turnover, the impact of denosumab on  
20 bone is highly consistent across a broad range of  
21 populations, including those with renal insufficiency,  
22 and is independent of fracture risk.

1           I've finished highlighting the clinical  
2 safety evaluation. These data have demonstrated  
3 significant increases in bone mineral density and,  
4 importantly, reductions in fracture risk. I'm going  
5 to spend the rest of my presentation highlighting the  
6 clinical safety evaluation.

7           This clinical safety evaluation was  
8 conducted with more than 13,000 patient years of  
9 follow up. I'm going to begin by summarizing overall  
10 adverse events and then highlight a number of  
11 prespecified adverse events of interest. Overall,  
12 adverse events were balanced between those receiving  
13 placebo and those receiving denosumab. The incidence  
14 of serious adverse events was 24.3 percent in subjects  
15 receiving placebo and 25.3 percent in those receiving  
16 denosumab. Withdrawals leading to study  
17 discontinuation or stopping study drug was unusual and  
18 balanced between the two groups.

19           There were 20 less deaths in those subjects  
20 receiving denosumab, and for that reason we decided to  
21 conduct a time-to-event analysis that's illustrated  
22 here.

1           As you can see with denosumab illustrated by  
2   the yellow line, the proportion of subjects surviving  
3   was greater in those receiving denosumab than placebo.  
4   The hazard ratio for death was .76 and although not  
5   statistically significant at a p-value of .08 was  
6   intriguing.

7           The overall adverse events in those subjects  
8   receiving hormone ablation therapy was similar,  
9   87 percent in those subjects receiving placebo and  
10   87.8 percent in those subjects receiving denosumab.  
11   Serious adverse events occurred in 27.6 percent of  
12   subjects receiving placebo and 31.6 percent of those  
13   subjects receiving denosumab. Again, withdrawals  
14   leading to study discontinuation or stopping of study  
15   drug were rare and balanced between the two groups.  
16   And as you can see, the overall incidence of death was  
17   similar between the two groups.

18           Now in order to better understand the impact  
19   of denosumab on disease progression in men with  
20   prostate cancer receiving androgen deprivation  
21   therapy, we conducted a prespecified analysis in order  
22   to assess the incidence of PSA rise, or prostate

1 specific antigen, which is an important marker of  
2 disease progression amongst men that demonstrated  
3 castrate levels of testosterone.

4           In this assessment, PSA was measured  
5 centrally in a prespecified schedule, and using the  
6 sensitive criteria that are illustrated on this slide,  
7 we demonstrated similar levels of PSA rises. In those  
8 subjects receiving placebo, PSA rises occurred in  
9 13 percent of subjects and 13.6 percent of subjects  
10 receiving denosumab.

11           In an additional analysis, that's described in  
12 the lower portion of this figure, the proportion of  
13 men that had a PSA rise greater than 5 was similar at  
14 all time points that PSA was assessed. These data  
15 suggest that denosumab does not have an impact on  
16 prostate cancer progression.

17           Now it's also important to look at survival,  
18 and we did a similar Kaplan-Meier analysis. And as  
19 you can see, the hazard ratio for death in those  
20 subjects receiving denosumab was the same as those  
21 subjects receiving placebo.

22           Now as I said, we had a number of adverse

1 events of interest that were prespecified. I'm going  
2 to describe in detail a number of these to you. There  
3 are two that have been highlighted in your briefing  
4 document that I won't detail, and that includes  
5 hypersensitivity where the event rates of adverse  
6 events that might be associated with hypersensitivity  
7 were balanced between those subjects receiving  
8 denosumab and those receiving placebo. I also won't  
9 detail the immunogenicity results as the incidence of  
10 binding antibodies was very low and there were no  
11 subjects that had antibodies that neutralized  
12 denosumab.

13           There were two adverse events that we  
14 observed over the course of the studies and I'll  
15 complete the safety presentation by highlighting  
16 those.

17           Now let's start with hypocalcemia. It's not  
18 unexpected that any drug that decreases bone  
19 resorption might result in reductions in serum  
20 calcium. Treatment with denosumab was associated with  
21 mild-to-moderate and transient decreases in calcium,  
22 which were less than 3 percent at month 1, and when we



1 did a careful assessment at the nadir of calcium at  
2 day 10, it was 3.1 percent. Calcium levels less than  
3 8 mg per deciliter were rare and were seen in less  
4 than 0.1 percent of subjects. They resolved  
5 spontaneously or with supplemental calcium. We  
6 observed no subjects with serum calcium levels below  
7 7. Symptomatic hypocalcemia was rare and was balanced  
8 between those subjects receiving denosumab and those  
9 subjects receiving placebo.

10 We looked carefully for any evidence of  
11 nonunion or delayed fracture healing. And as you can  
12 see in this table, these events were uncommon and were  
13 balanced between those subjects receiving denosumab  
14 and those receiving placebo.

15 Now we also sought to determine whether  
16 denosumab had any clinical impact on the immune  
17 system. As illustrated in this slide, the overall  
18 adverse events of infection were of similar frequency  
19 between those subjects receiving denosumab and those  
20 subjects receiving placebo. Serious adverse events of  
21 infection occurred in 3.4 percent of subjects  
22 receiving placebo and 4.3 percent of subjects

1 receiving denosumab, a difference that was not  
2 statistically significantly different.

3           Adverse events leading to study  
4 discontinuation occurred infrequently and fatal  
5 adverse events were similar between the two groups  
6 with 12 events in the placebo group and 6 events in  
7 the denosumab group.

8           Although there was no difference in overall  
9 adverse events, there were two adverse events that are  
10 worth comment. One is infective arthritis and the  
11 second is endocarditis. There were eight events that  
12 were coded to infective endocarditis in the denosumab  
13 group and none in the placebo group. It is important  
14 to note that none of these events were hospitalized  
15 nor did they receive IV antibiotics. And, therefore,  
16 it is unlikely that these were classic events of  
17 aseptic joint.

18           Although there were three cases of  
19 endocarditis in the PMO fracture study, there were  
20 also two cases of endocarditis in the HALT prostate  
21 cancer study demonstrating a similar frequency across  
22 the program.

1           Now in order to better understand the  
2 difference in serious adverse events of infection, we  
3 assessed the types of serious adverse events of  
4 infection that might account for this difference. We  
5 first looked at opportunistic infections, as one might  
6 hypothesize that a generalized immunosuppressive  
7 effect would result in an increase in the incidence of  
8 opportunistic infections, and as you can see from the  
9 table, opportunistic infections are well balanced  
10 between those subjects receiving placebo and those  
11 subjects receiving denosumab, suggesting that these  
12 data don't demonstrate an overall immunosuppressive  
13 effect of denosumab.

14           In order to assess what accounted for the  
15 numerical differences in serious adverse events of  
16 infection, we looked at each preferred term. And this  
17 slide illustrates the most common serious adverse  
18 events of infection.

19           It is important to note that pneumonia,  
20 which is the most common serious adverse event of  
21 infection, was well balanced between the two groups.  
22 In addition, sepsis, which would be probably the most

1 worrisome outcome of infection, is also of similar  
2 frequency between the two groups.

3           The majority of the numeric imbalance in the  
4 incidence of serious adverse events of infection was  
5 accounted for by adverse events of diverticulitis,  
6 infections of the urinary tract, and skin infections.  
7 We have provided a detailed analysis of the difference  
8 in the incidence of diverticulitis and urinary tract  
9 infections in your briefing document. Although I  
10 won't provide a detailed analysis in this  
11 presentation, I'm happy to answer any questions during  
12 the Q&A session.

13           What I'd like to do is focus on the  
14 difference in skin infections. Overall, skin  
15 infection adverse events were balanced between the two  
16 groups. However, there were more hospitalizations for  
17 skin infections in subjects receiving denosumab than  
18 subjects receiving placebo in women with  
19 postmenopausal osteoporosis. This slide illustrates  
20 the various types of skin infections that led to  
21 hospitalization. As you can see, the majority of  
22 these were comprised of cellulitis or erysipelas,

1    which on review of the case reports appear to be used  
2    interchangeably.

3               Now the majority of these skin infections  
4    were of the lower extremity, all but two. Fifty-four  
5    percent of the subjects who reported these events in  
6    the osteoporosis study had preexisting conditions that  
7    might place them at increased risk for lower extremity  
8    infections, including vascular disease or venous  
9    ulcers or skin wounds.

10              There was no predominant microbial agent  
11    that was identified. The mean hospital stay in those  
12    subjects receiving denosumab was four days and none of  
13    these subjects discontinued investigational product.  
14    There also didn't appear to be a relationship to the  
15    duration of treatment or the time since last dose, and  
16    it's important to note that there was only one  
17    recurrence despite continued therapy with denosumab.

18              So in summary, overall adverse events of  
19    infection were well balanced between the two groups.  
20    There was no evidence for an increased risk of  
21    opportunistic infections. Skin infections resulting  
22    in hospitalizations occurred in greater frequency in

1 denosumab treated subjects that had postmenopausal  
2 osteoporosis. Recurrent infections were infrequent  
3 despite continued RANK ligand inhibition, and,  
4 importantly, there was no increased risk of sepsis or  
5 death observed in those subjects treated with  
6 denosumab.

7           Now because RANK, RANK ligand, and OPG, the  
8 access has been speculated to play a role in vascular  
9 biology, we paid careful attention to whether or not  
10 denosumab might impact cardiovascular risk. All  
11 serious adverse events of cardiovascular nature were  
12 adjudicated by an external adjudication committee. As  
13 you can see from this slide, all cause mortality and  
14 cardiovascular death were lower in those subjects that  
15 received denosumab. And when one aggregates all  
16 cardiovascular events, the frequency and risk was  
17 identical between those receiving denosumab and those  
18 receiving placebo, suggesting that denosumab does not  
19 have an impact on cardiovascular risk.

20           Now because there has been an association  
21 between bisphosphonates and the development of  
22 osteonecrosis of the jaw, we paid careful attention

1 for the development of osteonecrosis. Potential cases  
2 were identified in the adverse event database using  
3 prespecified search criteria that were based on FDA  
4 advisory committee recommendations. Potential cases  
5 of osteonecrosis of the jaw were adjudicated by an  
6 external adjudication committee. There were no  
7 positively adjudicated cases of osteonecrosis jaw in  
8 either women with postmenopausal osteoporosis or in  
9 those subjects receiving hormone ablation therapy.

10 I'd like to spend a little bit of time  
11 highlighting data from our analysis of malignancy.  
12 Now both the FDA and Amgen use what's called the  
13 MedDRA coding system, which is the standard system  
14 that's used by the FDA and all pharmaceutical  
15 companies. Now the MedDRA coding system uses a  
16 hierarchal approach where at the highest level,  
17 adverse events are grouped by body location and don't  
18 really have a lot of pathophysiologic commonalities  
19 between these adverse events. This table uses these  
20 high level groupings. And, for example, if you look,  
21 for example, at reproductive neoplasms it includes a  
22 wide variety of neoplasms from uterine cancer to

1     ovarian cancer to vulvar cancer.

2                 When you look at these large groupings, you  
3     can see that there are numerical differences in the  
4     two groups and that would be expected in a randomized  
5     trial with some numerical differences favoring  
6     denosumab and some favoring placebo as highlighted in  
7     yellow.

8                 Now the system isn't really intended to  
9     provide a lot of clarity around clinical concepts, but  
10    instead is a way of organizing data. You can gain  
11    greater clarity by looking at the individual terms  
12    where there may be some small imbalances between the  
13    two groups.

14                In order to provide this sort of detail, I'm  
15    going to really drill down in five of these high level  
16    groupings. I'll begin by covering breast and then  
17    reproductive, gastrointestinal, endocrine, and  
18    hematologic. But before I begin, it's useful to note  
19    that I'm focusing on only those events which occurred  
20    at a greater frequency in the denosumab group. There  
21    were others that occurred at a greater frequency in  
22    the placebo group, such as malignant melanoma and lung



1 cancer, but these we felt were simply imbalances that  
2 were due to chance.

3           Now let's begin with breast cancer. In the  
4 PMO fracture study, we actually had a specific case  
5 report form to collect important and detailed  
6 information about prognostic factors with regard to  
7 breast cancer, because our preclinical data had  
8 actually suggested a protective effect of denosumab.

9           When we looked at this data, we were able to  
10 differentiate between those subjects that had new  
11 diagnosis of breast cancer versus those that were  
12 recurrences and that's illustrated here. You can see  
13 that 26 subjects in the placebo group and 28 subjects  
14 in the denosumab group had new diagnosis of breast  
15 cancer over the course of the study.

16           There were two recurrences of breast cancer  
17 in the placebo group and six in the denosumab group,  
18 but it's important to note, as is highlighted on this  
19 slide, that two of these recurrences in the denosumab  
20 group occurred during the first month of the study,  
21 suggesting that these recurrences were probably  
22 preexisting at the time that the subjects enrolled

1     into the study.

2                 Now it's also been highlighted that there  
3     were 20 subjects in the denosumab group and 10 in the  
4     placebo group that discontinued the study due to the  
5     adverse event of breast cancer. Now there are many  
6     reasons that subjects discontinue from clinical  
7     trials, but probably the most worrisome would be if  
8     there were some phenotypic difference between those  
9     breast cancers in the denosumab group and those in the  
10    placebo group.

11                As you can see, some of the important  
12    prognostic factors, including stage, node status, and  
13    histology are highlighted here and there doesn't  
14    appear to be any differences that would suggest poor  
15    prognostic factors in the breast cancers in the  
16    denosumab group.

17                Now let's turn and summarize the  
18    reproductive neoplasms that are highlighted here. As  
19    you can see, this large grouping includes a variety of  
20    neoplasms including uterine, ovarian, cervical, and  
21    vulvar. Endometrial or uterine cancers were similar  
22    in frequency between the two groups. There were five

1    ovarian neoplasms in the placebo group and 11 in the  
2    denosumab group. Two of those endocrine neoplasms in  
3    the denosumab group were benign cystadenomas resulting  
4    in five in the placebo group and nine in the denosumab  
5    group.

6           Cervical neoplasms occurred in one placebo  
7    subject and three subjects in the denosumab group.  
8    One of these cervical neoplasms was a carcinoma in  
9    situ in the denosumab group, resulting in one cervical  
10   cancer in the placebo group and two in the denosumab  
11   group.

12           Now if we look at the gastrointestinal  
13   neoplasms, you can see here that, again, they're  
14   comprised of a variety of different types of cancer.  
15   Colorectal cancers occurred with similar frequency.  
16   Pancreatic cancer occurred in three subjects in the  
17   placebo group and eight in the denosumab group.  
18   Gastric cancer occurred in three subjects in the  
19   placebo group, seven in the denosumab group, and  
20   esophageal cancer, oral cavity cancers, and a variety  
21   of miscellaneous gastrointestinal cancers occurred at  
22   the same frequency in the two groups.

1           With regard to endocrine neoplasms, this was  
2   comprised of thyroid neoplasms and carcinoid of the  
3   stomach. Thyroid neoplasms occurred in two subjects  
4   in the placebo group and six in the denosumab group.  
5   Of those neoplasms there were a number that were  
6   thyroid nodules, which were benign, two in the placebo  
7   group and four in the denosumab group, resulting in  
8   invasive thyroid cancers in two subjects in the  
9   denosumab group and none in the placebo group.

10           Now finally it was highlighted that there  
11   were three subjects with hemopoietic neoplasms in the  
12   denosumab group and none in the placebo group. And it  
13   is useful, perhaps, to walk through these three  
14   subjects.

15           The first subject had an adverse event of  
16   essential thrombocythemia. Now when we looked at the  
17   baseline laboratory values of this subject, you can  
18   see that the platelet count was 425,000, suggesting  
19   that this subject had preexisting thrombocythemia at  
20   study entry.

21           The second subject had a pseudolymphoma of  
22   the right shoulder. This was a polyclonal lymphoid

1 infiltrate that was in response to a tick bite. The  
2 subject was diagnosed with Lyme disease and after  
3 doxycycline therapy the event resolved.

4           Now the last subject had an adverse event of  
5 lymphoproliferation of B cells that was deemed by the  
6 investigator benign. When we looked at the baseline  
7 laboratory values, the white blood cell count was  
8 elevated on entry in the study and the last on study  
9 white blood cell count was 10.2 with 66 percent  
10 lymphocytes.

11           Now before I move on, I would like to  
12 highlight one additional issue. The FDA's briefing  
13 document highlighted that there were three subjects in  
14 our dose finding study that died of new malignancy.  
15 While it's understandable that there was concern  
16 regarding these deaths, it's important to keep in mind  
17 that this was a four year study with 412 subjects,  
18 with a mean age of 64. And there was a sevenfold more  
19 women that were randomized to receive denosumab than  
20 placebo, therefore it's not unexpected that there were  
21 more deaths in the denosumab group than the placebo  
22 group. Importantly, the overall incidence of

1 malignancies was well balanced between subjects in  
2 each group.

3           In summary, in our preclinical studies, RANK  
4 ligand inhibition did not promote cancer development  
5 or progression and these studies demonstrated that  
6 denosumab might have a beneficial effect. There was  
7 no statistical difference in the overall incidence of  
8 malignancies in the bone loss program. In the PMO  
9 fracture study there was no increased risk of death  
10 due to neoplasms, and similarly in the HALT prostate  
11 cancer study there was no increased risk due to death  
12 or due to neoplasms.

13           Now as I highlighted, there were two adverse  
14 events that were observed over the course of the  
15 study. The first was eczema adverse events.

16           Eczema was observed more frequently in the  
17 postmenopausal osteoporosis program with an incidence  
18 of 1.7 percent in the placebo group and 3.1 percent in  
19 the denosumab group. There were only two serious  
20 adverse events amongst these, 97 percent of these  
21 events were mild-to-moderate in severity. Only six  
22 subjects had recurrences despite continued therapy and

1 the mean duration of the events was 78 days in the  
2 denosumab group and 93 days in the placebo group.

3 The other adverse event that we observed  
4 over the course of the study was cataracts. Cataracts  
5 were observed more frequently in men with prostate  
6 cancer receiving androgen deprivation therapy with an  
7 incidence of 4.7 percent in these men treated with  
8 denosumab and 1.2 percent in subjects receiving  
9 placebo. We didn't observe this in women with  
10 postmenopausal osteoporosis.

11 It's important to note that the incidence of  
12 cataracts in the placebo group in the HALT prostate  
13 cancer study was actually quite low. It's also useful  
14 to point out that these cataracts were not identified  
15 by ophthalmologic exam and were just through adverse  
16 event reporting. And it appeared that most of these  
17 cataracts were actually cataract surgeries. There  
18 also is no known biological mechanism that might  
19 underlie this imbalance.

20 The data I've summarized for you from  
21 approximately 13,000 patient years of exposure to  
22 denosumab has demonstrated that denosumab has a

1 favorable safety profile. Overall, adverse events  
2 were mild-to-moderate in severity and were well  
3 balanced between the two groups. The overall  
4 incidence of eczema was observed more frequently in  
5 women with postmenopausal osteoporosis and cataracts  
6 were observed more frequently in men with prostate  
7 cancer receiving androgen deprivation therapy.  
8 Slightly more women with postmenopausal osteoporosis  
9 developed skin infections that required  
10 hospitalizations.

11           We believe that our analysis did not  
12 demonstrate an increased risk of malignancy or an  
13 overall immunosuppressive effect of the drug.  
14 However, we recognize that defining the safety profile  
15 is an ongoing process and we have designed a  
16 comprehensive program that includes clinical trials  
17 and observational studies to further define the safety  
18 profile.

19           So I'm now going to turn the podium back to  
20 Dr. Eisenberg who will detail this pharmacovigilance  
21 program that demonstrates our commitment to that end.

22           DR. EISENBERG: Thank you. We've presented



1 quite a bit of data. The last portion of the  
2 presentation is quite important, because as we think  
3 about pharmacovigilance, it really ideally should  
4 reflect continuous and comprehensive assessment of  
5 benefit/risks throughout a development program, as has  
6 been the case with denosumab.

7           As Dr. Lacey described, Amgen continues to  
8 use preclinical models as we have in the past to  
9 define the biology of RANK ligand inhibition. Work  
10 has gone on for about 15 years in this area and will  
11 continue to go on to understand the biology better.

12           The clinical development program  
13 Dr. Stehman-Breen described has been large,  
14 appropriately so, comprehensive, and included several  
15 approaches that we used to enhance detection of safety  
16 signals. We prespecified events of interest; we did  
17 that to ensure that we capture all potential events  
18 that occur in the areas that we discussed.

19           We had independent cardiovascular and ONJ  
20 adjudication committees to adjudicate the events as  
21 we've highlighted. And not surprisingly given the  
22 size of the program, we've observed small differences

1 in adverse events between both groups. And in each  
2 area of concern, we've looked to understand the  
3 clinical course and fully understand the potential  
4 safety signals.

5 In addition, the development program was  
6 appropriate for a program in bone loss, it utilizes  
7 biomarkers, imaging, and bone biopsy to characterize  
8 bone strength and bone quality.

9 I'm now going to describe a comprehensive  
10 pharmacovigilance program that we've planned that  
11 includes data from additional controlled clinical  
12 trials, long-term follow-up studies, and proactive  
13 safety surveillance.

14 Now the first issues I'd like to address are  
15 concerns specific generally to the safety of  
16 monoclonal antibodies. Monoclonal antibodies  
17 represent an evolution of the use of antibodies to  
18 inhibit therapeutic targets, which has evolved over  
19 many years. For example in women and children, many  
20 of you are familiar with RhoGAM, which is used to  
21 prevent Rh immune responses and there's a human  
22 monoclonal antibody recently, Synagis, that's noted in

1 the FDA's briefing documents, which was developed for  
2 the treatment of RSV infections in children.

3           Monoclonal antibodies also, as highlighted,  
4 have proved particularly useful in treating very  
5 serious diseases, cancer and autoimmune diseases,  
6 because they are very highly specific and efficacious  
7 in inhibiting their targets. But as I've highlighted  
8 here on this slide, a lot of the safety concerns  
9 specific to monoclonal antibodies have always related  
10 to their inhibition of the biologic target, but  
11 there's also been a concern historically with  
12 immunogenicity.

13           As we've moved from mouse antibodies to  
14 fully human antibodies, immunogenicity and  
15 hypersensitivity have become much less of a concern.  
16 With respect to denosumab, it's a fully human  
17 monoclonal antibody. And as Dr. Stehman-Breen  
18 commented, we've seen very little evidence of  
19 antibodies forming to denosumab, none that neutralize  
20 denosumab's activity and we haven't seen any  
21 difference in events that code to terms that are  
22 typical for hypersensitivity reactions.

1           Now as noted in FDA's briefing book, the  
2   main issue in terms of safety with monoclonal  
3   antibodies have been concerns that are attributable to  
4   the efficacy in inhibiting the target of therapy and  
5   I've given some examples here.

6           For example, the monoclonal antibody  
7   abciximab, which inhibits platelet function, has  
8   proved to be very effective in inhibiting thrombosis  
9   in cardiovascular disease. But it also has a bleeding  
10   risk, so it's clearly an on target effect, but it is a  
11   safety concern. Antibodies that have had important  
12   therapeutic benefits based on their potent effects in  
13   modulating immune responses such as Rituxan and  
14   Tysabri, have also turned out to have significant  
15   risks. One of the ones recently noted is progressive  
16   multifocal leukoencephalopathy, or PML, which is  
17   thought to be attributable to impaired immune response  
18   associated with the target of these therapies.

19           Similarly, other monoclonal antibodies have  
20   been associated with serious safety concerns and boxed  
21   warnings as a consequence of their efficacy in  
22   inhibiting their targets, but they remain important

1 therapeutic agents because of their profound efficacy  
2 for a critical illness.

3           So what about denosumab? What do we know  
4 about RANK ligand inhibition? Dr. Lacey highlighted  
5 the preclinical data that supported the development of  
6 denosumab. The predominant effect in adult  
7 preclinical models and in our clinical development  
8 program is the reduction in bone resorption with  
9 expected increases in bone mineral density and bone  
10 strength. Although there is no evidence of an adverse  
11 effect on bone due to long-term inhibition of RANK  
12 ligand, it will be important to ensure that there is  
13 long-term follow up of patients treated with denosumab  
14 to better understand the benefit/risk of long-term  
15 inhibition and bone resorption by this mechanism.

16           Now the preclinical data and clinical  
17 studies do not suggest a broad immunosuppressive  
18 effect of RANK ligand inhibition. Nonetheless, there  
19 have been signals of increased infections in patients  
20 treated with denosumab. As noted in the briefing book  
21 and Dr. Stehman-Breen's presentation, what we know is  
22 there does not appear to be an increased risk of

1 opportunistic or viral infections, which is  
2 inconsistent with any impact on cell mediated  
3 immunity.

4 Overall, as we've noted, there are small  
5 differences in common bacterial infections, but not  
6 with respect to severity, rate of sepsis, or deaths  
7 due to infection. These may be due to chance, but  
8 with respect to the increased risk of hospitalization  
9 due to skin infection, we've had more of a concern  
10 since the etiology may reflect factors other than  
11 susceptibility to a bacterial infection.

12 If it is a real signal it is possible that  
13 there is a relationship to a skin specific response  
14 such as an increased inflammatory response perhaps  
15 relating to the signal we saw of increased adverse  
16 events of eczema.

17 Since RANK ligand is expressed in skin  
18 immune cells this is possibly an on target effect, we  
19 can't exclude that, and Amgen continues to monitor the  
20 risk of infection in our clinical trials to determine  
21 whether there may be a modest risk related to RANK  
22 ligand inhibition.

1                   Now with respect to malignancy, inhibition  
2   of RANK ligand is not expected to have any tumor  
3   promoting effects. And in our clinical trials,  
4   overall there was no statistically significant  
5   difference in the overall adverse events of  
6   malignancy.

7                   Dr. Stehman-Breen reviewed the results of  
8   the safety analysis and the small imbalances observed  
9   with some tumor types, which do not suggest an  
10  increased risk of malignancy in patients treated with  
11  denosumab.

12                  Importantly there was also no increase in  
13  deaths related to malignancy and, overall, the rates  
14  of malignancy that we observed in this clinical  
15  program are within the range expected in the patient  
16  populations we studied and when compared to other  
17  clinical trials in similar populations.

18                  Finally, the expectation based on  
19  preclinical models was, in fact, there was a potential  
20  for denosumab to prevent tumor metastasis to bone and  
21  that is currently being studied in an extensive  
22  placebo controlled clinical program.

1           In summary, the expected effect of denosumab  
2   inhibition on RANK ligand is decreased bone resorption  
3   and our clinical data has suggested that there may be  
4   an altered skin immune reactivity in some patients.

5           Now I'd like to turn my attention to risk  
6   assessment, because we have a particularly robust  
7   program and we take the view that risk assessment  
8   continues throughout the life of a drug in the market  
9   no matter how comprehensive the clinical development  
10   program.

11           The risk assessment program plan for  
12   denosumab also reflects the additional vigilance  
13   appropriate for a therapeutic with a novel mechanism  
14   of action. This includes additional placebo  
15   controlled trials that offer the highest level of  
16   evidence for ascertainment of safety signals, long-  
17   term follow up of patients that have been in our  
18   clinical trials, and proactive safety surveillance.

19           Now we've studied a wide variety of patients  
20   in the clinical trials with denosumab and they're  
21   representative of the patient's that we anticipate  
22   would be treated in clinical practice. However, we do



1 note that these were placebo controlled trials, and as  
2 a consequence we tended to include lower risk patients  
3 at least with respect to fracture risk. However, the  
4 benefits of denosumab in terms of fracture prevention,  
5 as you've seen in Dr. Stehman-Breen's presentation,  
6 were consistent across all subgroups. There were very  
7 few exclusions relating to comorbidity, and as we've  
8 noted, denosumab was used even in patients with  
9 significant renal impairment.

10           The adverse reactions that we observed are  
11 listed here, and, in addition, although not confirmed  
12 in the development program, there are adverse events  
13 of interest that we think continue to need to be  
14 assessed and I'll detail how we propose to do this.

15           I do want to comment very briefly and  
16 specifically on osteonecrosis of jaw or ONJ. We have  
17 and continue to use an independent expert panel to  
18 evaluate potential cases of ONJ. Although there were  
19 no cases observed in the postmenopausal osteoporosis  
20 trial or the HALT indication studies, we have observed  
21 in the advanced cancer studies, where we use a 12-fold  
22 higher dose of denosumab in comparison to zoledronic

1 acid in those studies, we have observed cases of ONJ.  
2 This is consistent with the known risk of ONJ in  
3 patient with advanced cancer and our data suggests  
4 that inhibition of bone resorption is an important  
5 factor. We continue to assess ONJ with this  
6 independent panel in all our clinical programs.

7           The long-term safety in patients with  
8 postmenopausal osteoporosis includes extension studies  
9 of our Phase 2 and 3 programs. Out of our Phase 2,  
10 216 study, patients will be followed up for up to 10  
11 years; 45 of 150 patients are currently being  
12 followed, and I think these studies in particular will  
13 be useful in assessing for long-term fracture risk and  
14 events of interest that I've highlighted.

15           There's also an ongoing placebo controlled  
16 study in Japan, which is noted on this slide, which  
17 also includes an alendronate arm, a much smaller study  
18 than our 216 study, but again will provide important  
19 safety data and this study will be completed in 2012.

20           Now we've planned an unusually large  
21 postmarketing observational study that I'd like to  
22 discuss now and this is part of the safety

1 surveillance program that's designed to accrue data on  
2 up to 380,000 patients over at least five years. The  
3 observational study would include accruing both the  
4 380,000 patients who are treated with denosumab and a  
5 similar number of patients treated with other  
6 therapies, so over 700,000 patients in total.

7           Now to accomplish this, we've identified  
8 several health care databases which I've shown on this  
9 slide. We have experience in collaborating with the  
10 academic groups that access these databases and we  
11 believe we will be able to collect the data that will  
12 define whether there are increased events of interest  
13 that I've talked about in denosumab compared with  
14 other therapies.

15           Now how do we approach this? Of particular  
16 value, for example, are databases such as the Nordic  
17 database, which are electronic medical record  
18 databases, so in that database one can get x-rays for  
19 ascertainment, for example, of an atypical fracture or  
20 a subtrochanteric fracture. The specific design of  
21 this study and the selection of appropriate database  
22 are in progress and will reflect these concerns, and

1 clearly, as well, how our discussions in terms of the  
2 clinical implementation proceed with FDA.

3           Now observational studies have well  
4 recognized limitations in detecting safety signals.  
5 Our study recognizes these issues and is focused on  
6 assessment of specific safety signals that should be  
7 informed by the observational approach. For example,  
8 long-term safety surveillance is useful in detecting  
9 rare events that would otherwise be unexpected in the  
10 population of interest, so the selection of the number  
11 380,000 based on what we call the rule of three means  
12 we should be able to detect events down to 1 in  
13 100,000. This is useful if we're looking for unusual  
14 malignancies, and as I've highlighted, we may be able  
15 to get data on unusual types of fractures.

16           Another issue with observational studies is  
17 that they may be confounded by underlying illnesses  
18 and factors that would favor one treatment or another.  
19 Nonetheless, useful comparative rates between  
20 treatments can be assessed for events such as overall  
21 risks of fractures and rates of severe or  
22 opportunistic infections. These databases I want to

1 specifically note are not useful when there are high  
2 expected background rates of disease. So for example,  
3 cardiovascular disease risk must be assessed as we've  
4 done in a randomized clinical trial.

5           Finally, with respect to malignancies, we  
6 can take advantages I've noted in the last bullet of  
7 the National Cancer Institute cancer database to  
8 compare relative rates in treatment with denosumab  
9 long-term, other therapies, to standardized expected  
10 rates.

11           Overall, the combination of long-term  
12 follow-up studies, additional clinical trials, and  
13 proactive surveillance using these databases provides  
14 a comprehensive pharmacovigilance program that will  
15 support the use of denosumab in patients with  
16 postmenopausal osteoporosis.

17           Now in patients treated with hormone  
18 ablation therapies for breast and prostate cancer,  
19 both programs include long-term follow up, as I've  
20 highlighted, which is off treatment for the breast  
21 cancer patients and on and off treatment in the  
22 prostate cancer patients. In postmenopausal women

1 treated with aromatase inhibitors for breast cancer,  
2 there was considerable interest as we've discussed in  
3 determining whether the preclinical data suggesting a  
4 benefit in terms of breast cancer outcomes could be  
5 confirmed clinically.

6           The Phase 3 study I've shown on this slide  
7 is being carried out by the Austrian Breast Cancer  
8 Study Group and it's designed to answer these  
9 questions. This study has enrolled 1200 of 2800  
10 patients who will be followed for at least six years  
11 for the primary outcome of fracture prevention, but in  
12 addition there are endpoints related to the risk of  
13 cancer recurrence.

14           The cataract issue requires a dedicated  
15 study, and since we did observe cataracts in men  
16 treated with androgen deprivation, we have designed  
17 and have initiated a dedicated ophthalmologic study,  
18 which is placebo controlled, and in the at risk  
19 population and will be completed by 2011 to  
20 definitively assess this risk.

21           I would like to now briefly comment on  
22 another important aspect of Amgen's overall

1 development program for denosumab, but independent of  
2 the program we're discussing today. Because bone  
3 resorption is required in the progression of  
4 metastatic bone disease, denosumab is being studied in  
5 patients with advanced cancer with bone metastasis.

6 Phase 2 studies identified the appropriate  
7 dose for these Phase 3 studies as a 12-fold higher  
8 dose of denosumab in terms of its efficacy. This is  
9 what is being tested and compared with zoledronic acid  
10 in the three studies I have illustrated on this slide.

11 The breast and solid tumor studies recently  
12 completed, and we did disclose these, the analysis is  
13 still ongoing, I've simply highlighted from a safety  
14 perspective that the overall survival in these studies  
15 compared to the zoledronic acid for patients treated  
16 with denosumab was similar. And as I've noted, these  
17 patients were treated with a dose that's, in this  
18 case, of a 120 milligrams Q monthly subcutaneously. I  
19 do want to highlight that these data have not yet been  
20 reviewed or submitted to FDA.

21 In addition, based on our preclinical data,  
22 denosumab is being studied at the higher doses in

1 prevention of bone metastasis in placebo controlled  
2 studies of prostate and breast cancer patients. The  
3 prostate study is fully enrolled, that's the second  
4 one from the bottom, and will complete four years of  
5 follow-up next year and report out. The breast cancer  
6 study is planned to start later this year, and these  
7 studies will provide additional data of denosumab  
8 effects on at least tumor progression as it relates to  
9 general tumor outcomes.

10           So to summarize, the benefit/risk of  
11 denosumab in patients with cancer to prevent  
12 complications of bone loss is supported by additional  
13 studies and other programs characterizing higher doses  
14 of denosumab to treat patients with metastatic bone  
15 disease.

16           I'd like to now turn my attention to the  
17 minimization of potential risk through risk  
18 communication to prescribers and patients. Risk  
19 communication is the foundation of risk minimization.  
20 With respect to the risks of denosumab in the clinical  
21 development program, there are safety issues that can  
22 be minimized through labeling. The most important is



1    hypocalcemia, which while expected for an  
2    antiresorptive agent has the potential to be  
3    clinically meaningful. Therefore labeling should  
4    contraindicate use in patients with uncontrolled  
5    hypocalcemia and would recommend Vitamin D and calcium  
6    supplementation in patients who are treated with  
7    denosumab.

8            Although ONJ has not been observed in this  
9    clinical program, it is a potential serious risk that  
10   has been a concern with bisphosphonates and has been  
11   observed in the advanced cancer studies. There is  
12   evidence that communication of this risk and the need  
13   for good dental hygiene may be of value in minimizing  
14   risks. The risk of hospitalization with skin  
15   infections is also amenable to risk minimization  
16   through labeling.

17           Other risks that have been observed clearly  
18   need to be communicated, recognizing that  
19   communication may not minimize the risk. Similarly,  
20   communication of theoretical risks in some instances  
21   may be appropriate, but only to inform prescribers and  
22   patients, not to minimize risk. Amgen is committed to

1 working closely with FDA to develop the appropriate  
2 risk communication plan.

3           In terms of clinical use, there are several  
4 aspects I want to highlight. Denosumab is  
5 administered as a 60 mg subcutaneous injection every  
6 six months. Dosing adjustments are not required, and  
7 in contrast to some of the bisphosphonates, denosumab  
8 can be used with significant renal dysfunction.  
9 Injections of denosumab are well tolerated and not  
10 associated with acute reactions.

11           Denosumab should be administered by health  
12 care professional to ensure the full dose is properly  
13 injected. Administration in this manner supports  
14 oversight by physicians of adherence to the prescribed  
15 six month regimen, which is important since the  
16 benefits of denosumab are reversible.

17           Amgen plans to support patients and  
18 prescribers with reminder systems to facilitate  
19 adherence. It's also important to note that in  
20 clinical trials, dosing of denosumab could occur one  
21 month prior or after the six month prescribed  
22 injection date, so there is flexibility in scheduling

1 treatment. Amgen also plans to support patient  
2 adherence once they've started on denosumab with an  
3 assistance program as appropriate.

4           Now we've presented a great deal of data  
5 from a comprehensive program that led to the  
6 development of denosumab as a therapeutic agent. We  
7 recognize that there are some areas of scientific  
8 controversy with respect to RANK ligand biology, but  
9 our data are clear with respect to the benefits in  
10 reducing bone resorption, increasing bone mineral  
11 density, and preventing fractures.

12           We look forward to the opportunity to  
13 further review the data we've presented with the  
14 committee. With respect to the indications we're  
15 seeking, the data demonstrated benefit for the  
16 prevention of osteoporosis and fractures in women with  
17 postmenopausal osteoporosis, supporting the treatment  
18 and prevention indications. And as Dr. Siris noted,  
19 postmenopausal osteoporosis represents an important  
20 health care concern for women, for which there remains  
21 a need for alternative therapies, one that denosumab  
22 can satisfy.

1           The overall safety profile of denosumab  
2 compares favorably to other approved classes of agents  
3 for these indications and efficacy in some instances  
4 appears superior. In postmenopausal women with breast  
5 cancer treated with aromatase inhibitors, clinicians  
6 have recognized the need to prevent bone loss  
7 associated with treatment and there are no currently  
8 approved therapies.

9           In men with prostate cancer with androgen  
10 deprivation, the impact of bone loss and fractures on  
11 patient outcome has also been recognized. In both  
12 populations, denosumab demonstrated efficacy in  
13 reducing bone loss and in the prostate cancer patients  
14 in preventing fractures.

15           In addition to the programs supporting the  
16 regulatory requirements for approval for these  
17 indications, we have ongoing and planned studies and a  
18 pharmacovigilance program that will support the  
19 benefit/risk of denosumab long-term.

20           We appreciate the opportunity to review our  
21 data with you and look forward to the panel's  
22 comments. Thank you.

1 DR. CARSON: Thank you very much and thank  
2 your whole team for the excellent materials you've  
3 prepared for us and a very organized presentation  
4 today. Also, I hope you'll express and extend our  
5 appreciation to those many, many clinical  
6 investigators who helped you gather your data. And  
7 maybe the press can help us all today thank those  
8 thousands of men with prostate cancer, hundreds of  
9 women with breast cancer, and many, many  
10 postmenopausal women with bone loss who three years  
11 ago and more took an unknown risk for an unknown  
12 benefit and donated a lot of their time to help the  
13 team present this data today.

14 Now we will take a short break. Committee  
15 members please remember there should be no discussion  
16 of any of the meeting topics during the break amongst  
17 yourselves or any members of the audience. We'll  
18 resume at 10:05. Thanks.

19 (Whereupon, a recess is taken.)

20 DR. CARSON: The FDA's presentations will  
21 begin with Dr. Popat.

22 DR. POPAT: Welcome back. I am Vaishali

1 Popat. I am a medical officer at FDA in the  
2 Division of Reproductive and Urologic Products. I will  
3 present the FDA analysis on the notion of efficacy.

4           The focus of our efficacy and safety  
5 presentations includes the Dose-Finding Trial 223, the  
6 primary efficacy trial for each of the four  
7 indications and Trial 234, which evaluated patients  
8 previously on alendronate, who were switched to  
9 denosumab or continued on alendronate. We will be  
10 discussing only safety issues with Trial 234.

11           Prior to discussing individual primary  
12 efficacy trials, I will briefly talk about  
13 pharmacometric profile and dose selection. The  
14 pharmacometric profile of denosumab has been  
15 evaluated, and it reveals that denosumab is 61 percent  
16 bio-available. The half-life is 25 days. There is no  
17 accumulation.

18           Similar pharmacokinetic profile is observed  
19 across different population groups. The PK profile is  
20 not affected by age, weight, gender, race or renal  
21 function. And pharmacokinetic analysis showed that a  
22 single dose is adequate -- single fixed dose is

1 adequate. Weight did not affect the fracture or BMD  
2 efficacy.

3           So the Trial 223 is a dose-finding trial.  
4 This was a four-year randomized placebo and active  
5 control trial of postmenopausal women with low bone  
6 mass. The primary efficacy endpoint was lumbar spine  
7 BMD at 12 months. Nine treatment cohorts were  
8 evaluated with 40 to 50 subjects per cohort. These  
9 cohorts were placebo; denosumab 6 milligrams,  
10 14 milligrams or 30 milligrams Q3months or  
11 14 milligrams, 60 milligrams, 100 milligrams and 240  
12 milligrams Q6months, and 70 milligrams alendronate  
13 once weekly. The 70 milligrams once weekly  
14 alendronate dose is the dose for treatment of  
15 postmenopausal osteoporosis.

16           The annual population was predominantly  
17 Caucasian with mean age of 63; 64 percent of those  
18 enrolled completed the trial.

19           The results of the primary efficacy endpoint  
20 of change in lumbar spine BMD are presented in this  
21 table. The dose groups are arranged by the yearly  
22 dose received. All those groups achieved increased

1 lumbar spine BMD at month 12. The 100 milligrams  
2 Q6months and 210 milligrams Q6months did not achieve  
3 better BMD response than the 60 milligrams Q6months.  
4 The sponsors selected only one dose, 60 milligrams  
5 Q6months, highlighted in this light blue to take into  
6 Phase 3.

7           The primary efficacy trial for the treatment  
8 of osteoporosis indication is Trial 216. This was a  
9 randomized, double-blind, placebo-controlled, three-  
10 year trial in postmenopausal women with osteoporosis.  
11 The primary endpoint was subject incidence of new  
12 morphometric vertebral fractures at three years.  
13 Secondary endpoints were timed to first nonvertebral  
14 fracture and time to first hip fracture. Important  
15 tertiary endpoints were change in lumbar spine and hip  
16 BMD.

17           Overall, 7,808 subjects were randomized; 46  
18 subjects did not receive investigational product, and  
19 86 percent of the population completed the trial.

20           The trial participants were predominantly  
21 Caucasian with a mean age of 72 years. The baseline  
22 lumbar spine BMD T score were minus 2.8 and 23 percent



1 of the population had a vertebral fracture at  
2 baseline. A post hoc analysis doing the FRAX  
3 calculator was performed and 10-year major  
4 osteoporotic risk for the fracture was 19 percent, and  
5 10-year hip fracture risk was 7 percent.

6 For the primary efficacy endpoint of new  
7 vertebral fractures, treatment with denosumab  
8 demonstrated 4.8 percent absolute risk reduction and  
9 68 percent relative risk reduction at month 36 with a  
10 p-value of less than 0.001.

11 For the secondary efficacy endpoint,  
12 nonvertebral fracture, treatment with denosumab  
13 resulted in 1.5 percent absolute risk reduction and  
14 20 percent relative risk reduction with a p-value of  
15 0.0106.

16 For another secondary endpoint, hip  
17 fractures, the treatment with denosumab resulted in  
18 .3 percent absolute risk reduction and 40 percent  
19 relative risk reduction. The relative risk reduction  
20 p-value was 0.036. It should be noted that for the  
21 absolute risk reduction, the confidence interval  
22 crosses zero.

1           In the ongoing review, to evaluate this  
2 further, we looked at the incidence of hip fractures  
3 for each year of the study. So this slide shows the  
4 accrued incidence of hip fractures within each  
5 one-year time interval of this three-year study. It's  
6 not a cumulative incidence.

7           So it's noteworthy that in year 1 and 2 --  
8 in year 1, the placebo incidence is .5 and denosumab  
9 is .3. So denosumab is lower than placebo. In  
10 year 2, it's .4 versus .1. So again, it's lower than  
11 placebo. However, in year 3, the incidence climbs  
12 back to the similar rate as placebo.

13           We recognize that the number of fractures is  
14 small, but because of this hip fracture finding noted  
15 in year 3, we looked further to see if the same trend  
16 occurred with nonvertebral and vertebral fractures.

17           So this slide shows the accrued incidence of  
18 nonvertebral fractures and vertebral fractures.  
19 Again, this is by year. It's not a cumulative  
20 incidence. So incidence of nonvertebral fracture was  
21 greater in placebo group from all time intervals  
22 compared to denosumab. And there was no change in the

1 new nonvertebral fracture incidence rates between  
2 year 2 and year 3.

3           For vertebral fractures, the incidence was  
4 greater in placebo group in all three years compared  
5 to placebo. We also note that the incidence of new  
6 vertebral fractures was similar in year 1 and 2. In  
7 year 3, the incidence was higher than 1 and 2.

8           Although a tertiary endpoint, the changing  
9 BMD at lumbar spine and total hip, they're an  
10 important endpoint to discuss. And it is the primary  
11 endpoint for all the other trials to be discussed  
12 today.

13           At the lumbar spine, the treatment  
14 difference at month 36 was 8.8 percent increasing BMD,  
15 and for total hip, the treatment different at month 36  
16 was 6.4 percent increase in BMD. These numbers come  
17 from the whole trial population, not the substudy.

18           Another supportive measure of efficacy are  
19 bone turnover markers. CTX is a marker of bone  
20 resorption. This graph outlines the percent change in  
21 CTX levels over time. Treatment in denosumab resulted  
22 in marked suppression of serum CTX levels. The nadir

1 in CTX appears to occur one to three months following  
2 the denosumab dose, a time when denosumab effect is  
3 likely maximal. Before the next dose, CTX levels  
4 begin to trend back towards baseline.

5 Bone remodeling includes bone resorption and  
6 bone formation. Bone resorption and bone formation  
7 are tightly coupled processes. With denosumab  
8 therapy, the marker of bone formation, P1NP, lagged  
9 behind CTX but followed a similar pattern.

10 In our evaluation of the CTX effect, it was  
11 noted that some patients had levels of CTX that were  
12 undetectable or below the lower limit of  
13 quantification. This finding was most notable at the  
14 anticipated time of maximal denosumab effect. In this  
15 table, the blue highlighted columns represent the  
16 visits one, two, three months following denosumab  
17 doses, a time at which the nadir occurs.

18 At these time points, CTX was undetectable  
19 in 39 to 68 percent of subjects treated with  
20 denosumab. Similarly, the marker of bone formation,  
21 P1NP, was also undetectable in 24 to 36 percent of the  
22 subjects treated with denosumab at month 6 onward with

1 the highest number of subjects with undetectable  
2 levels at month 36.

3           In their evaluation of the person's changing  
4 CTX, the sponsor said the CTX level for subjects with  
5 undetectable levels to the lower limit of  
6 quantification was 0.049. We were concerned that this  
7 approach may underestimate CTX suppression in subjects  
8 treated with denosumab. So we conducted an evaluation  
9 of change in CTX based on three scenarios: one,  
10 undetectable CTX levels set to the lower limit of  
11 qualification which is 0.049 in the blue line. The  
12 red line represents the CTX levels set to half the  
13 lower limit of quantification which is 0.025 and the  
14 green line represents undetectable levels set to zero.

15           So this graph shows the results for the  
16 change in CTX with denosumab therapy in the first year  
17 of the trial based on these three scenarios. From  
18 this analysis, we can only conclude that the decrease  
19 in serum CTX levels one month after denosumab dosing  
20 was in the range of 87 percent to 94 percent. It  
21 should be noted that this degree of suppression of  
22 bone resorption markers has not been seen before with

1 any other anti-resorptive agent.

2           Trial 132 was the primary efficacy trial for  
3 the osteoporosis prevention indication. This was a  
4 randomized, double-blind, placebo-controlled, four-  
5 year trial with two years of active treatment and two  
6 years of follow-up off treatment in postmenopausal  
7 women with low bone mass. The primary efficacy  
8 endpoint was person changed from baseline in lumbar  
9 spine BMD at 24 months. Secondary endpoints were  
10 persons changed from baseline in BMD of the hip,  
11 distal radius and total body.

12           Overall, 332 subjects were randomized.  
13 Three subjects did not receive investigational  
14 product, and 87 percent of the population completed  
15 the trial.

16           The baseline characteristics of the  
17 population enrolled in this trial reflect the intended  
18 population for the prevention of osteoporosis  
19 indication. They are younger women. The mean age is  
20 59 years with a bone mineral density that is low but  
21 not in the osteoporotic range. These subjects don't  
22 have a history of osteoporotic fracture and because of

1 their young age, their fracture risk tends to be low.

2 In this population, the treatment difference  
3 at month 24, which was the primary efficacy endpoint,  
4 for lumbar spine following the denosumab therapy was  
5 7 percent. Total hip was the secondary efficacy  
6 endpoint, and the treatment difference at month 24 was  
7 4.5 percent with a p-value of less than 0.001.

8 With many therapies that are used for  
9 treatment of chronic disease, such as osteoporosis,  
10 the durability of effect after cessation of therapy is  
11 important to understand. In Trial 132, subjects were  
12 on therapy for the first two years and then followed  
13 off therapy for the last two years. This graph shows  
14 change in bone mineral density from baseline across  
15 this four years.

16 During the first two years of the treatment,  
17 lumbar spine BMD increased continuously. However, off  
18 treatment, it rapidly returned to baseline in the next  
19 two years. The same thing happened for the total hip  
20 BMD.

21 We looked at the BMD results. The fracture  
22 is also an important -- it's actually the main

1 interest. So we also looked at the fracture incidence  
2 during this off treatment phase because of the rapid  
3 decline in the BMD. So the number of fractures  
4 occurring the off treatment phase was small. There  
5 were five fractures in the placebo group and nine  
6 fractures in the denosumab group.

7 Trial 135 is the primary efficacy trial for  
8 the prevention and treatment of bone loss in patients  
9 undergoing hormone ablation for breast cancer  
10 indication. This trial was randomized, double-blind,  
11 placebo-controlled, four-year trial with two years  
12 active treatment and two years off treatment in women  
13 receiving aromatase inhibitor therapy for breast  
14 cancer who have low bone mass.

15 The primary efficacy endpoint was person  
16 changed from baseline in lumbar spine BMD at 12  
17 months. Secondary efficacy endpoints were person  
18 changed from baseline in BMD of the hip, distal radius  
19 and total body. Exploratory efficacy endpoint  
20 included overall survival at month 24.

21 A total of 252 women were randomized. Three  
22 subjects did not receive investigational product, and



1 81 percent completed the trial. Subjects were  
2 predominantly Caucasian and similar to the  
3 osteoporosis prevention population. The breast cancer  
4 population mean age was 59 years.

5 Bone mineral density was minus 1.1 at lumbar  
6 spine. Only 1 percent of the population actually met  
7 the criteria for osteoporosis at baseline. The  
8 baseline characteristics of the breast cancer include  
9 time since diagnosis of three years and 65 percent  
10 have been on aromatase inhibitor therapy for at least  
11 six months.

12 Most subjects had Stage 1 or 2 cancer based  
13 on American Joint Committee on Cancer Criteria;  
14 98 percent has estrogen receptor positive tumor while  
15 83 percent were progesterone receptor positive.  
16 HER2/neu status was negative in 65 percent of  
17 patients. The history of prior breast cancer  
18 therapies were well balanced between the groups.

19 In this population, the treatment difference  
20 at month 12, which was the primary efficacy endpoint,  
21 following the denosumab therapy was 5.5 percent at  
22 lumbar spine and 3.7 percent at total hip.

1           Trial 138 is the primary efficacy trial for  
2 the prevention and treatment of bone loss in patients  
3 undergoing androgen deprivation therapy for prostate  
4 cancer indications. This was a randomized,  
5 double-blind, placebo-controlled, five-year trial with  
6 three years active treatment and two years off  
7 treatment in men undergoing androgen deprivation  
8 therapy for prostate cancer.

9           Enrollees were either more than or equal to  
10 70 years of age or if they were less than 70 years,  
11 then they would have to have low bone mass or a  
12 history of osteoporotic fracture.

13           The primary endpoint was person changed from  
14 baseline in lumbar spine BMD at 24 months. Secondary  
15 endpoints were person changed from baseline in BMD of  
16 the hip, incidence of any fracture, incidence of new  
17 morphometric vertebral fracture. Exploratory endpoint  
18 included overall survival at month 36.

19           A total of 1468 men were randomized. Twelve  
20 subjects did not receive investigational product, and  
21 62 percent completed the trial. Trial participants  
22 were predominantly Caucasian with the mean age of 75

1 years. Bone mineral density was normal. Recall that  
2 in this trial, patients were eligible for enrollment  
3 if they were over age 70, regardless of their BMD  
4 status; 83 percent of the subjects were over age 70;  
5 23 percent had a vertebral fracture at baseline. Mean  
6 duration of androgen deprivation therapy was 33  
7 months.

8           The baseline characteristic of the prostate  
9 cancer include a mean time since diagnosis of five  
10 years. Most subjects had Stage 2 cancer based on  
11 National Comprehensive Cancer Network scoring and a  
12 Gleason score of 7 or below. Approximately half did  
13 not receive primary cancer therapy. History of  
14 radiation surgery and chemical castration were similar  
15 in both groups.

16           In this population, treatment difference at  
17 month 24, which is the predefined endpoint, following  
18 denosumab therapy was 6.7 percent at lumbar spine and  
19 4.8 percent at total hip. Treatment with denosumab  
20 demonstrated a 2 percent absolute risk reduction and  
21 28 percent relative risk reduction in any fracture.  
22 This was not significant. However, for new vertebral

1 fracture, the treatment with denosumab resulted in 2.4  
2 percent absolute risk reduction and 62 percent  
3 relative risk reduction, and this was with a p-value  
4 of 0.0125.

5           So in summary, for fracture efficacy,  
6 denosumab 60 milligrams every six months was effective  
7 in decreasing the incidence of fractures in  
8 postmenopausal osteoporotic women. However, we note  
9 the incidence of hip fracture was lower than placebo  
10 in the first and second year but became similar to  
11 placebo in the third year of the primary fracture  
12 trial.

13           For the BMD, treatment with denosumab  
14 resulted in increase in the populations evaluated,  
15 including postmenopausal women with osteoporosis and  
16 low bone mass, women with low bone mass receiving  
17 aromatase inhibitor therapy for breast cancer, and men  
18 undergoing androgen deprivation therapy for prostate  
19 cancer.

20           There is profound suppression in markers of  
21 bone resorption. Once treatment with denosumab is  
22 discontinued, BMD quickly returns to baseline.

1           Now, I will turn the podium over to my  
2   colleague, Adrienne Rothstein, who will present the  
3   safety analysis.

4           DR. ROTHSTEIN: Good morning, my name is  
5   Adrienne Rothstein. I'm a clinical reviewer in the  
6   Division of Reproductive and Urologic Products, and  
7   I'll be presenting the FDA's safety analysis of  
8   denosumab.

9           For this safety analysis, we reviewed case  
10   narratives, adverse events terms reported by the  
11   investigator and reviewed the medical coding by the  
12   applicant. We also had assistance from our  
13   specialized quantitative safety pharmacoepidemiology  
14   team to help evaluate adverse events of special  
15   interest.

16           Throughout this safety review, serious  
17   adverse events or SAEs refers to adverse events that  
18   meet the regulatory definition of serious, which is  
19   defined as an event that results in any of the  
20   following outcomes: death, life-threatening life  
21   adverse event or inpatient hospitalization or  
22   prolongation of existing hospitalization, persistent

1 or significant disability or an important medical  
2 event that required an intervention to prevent these  
3 serious outcomes.

4 Our safety review focused on four primary  
5 key studies, 216, 132, 135 and 138, which have been  
6 previously described. The PMO safety population  
7 included 8,091 subjects. The HALT safety population  
8 included 1,705 subjects.

9 When we look at overall adverse event rates  
10 for the primary postmenopausal osteoporosis trials,  
11 the number of deaths in the placebo group was higher  
12 than in the denosumab group in Trial 216, and there  
13 were no deaths in Trial 132. Serious adverse events  
14 were balanced in Trial 216; however, denosumab  
15 subjects in Trial 132 had a higher incidence of  
16 serious adverse events. Adverse events that led to  
17 trial withdrawal or investigational product  
18 discontinuation and overall adverse rates did not  
19 differ between the treatment groups for either trial.

20 In the primary hormone ablation trials,  
21 deaths were balanced across both treatments groups.  
22 There was a higher rate of serious adverse events in

1 subjects receiving denosumab in both trials. The  
2 incidence of adverse events that led to withdrawal  
3 from the trial, discontinuation of investigational  
4 product and the overall adverse event profile were  
5 similar across both treatment groups in these studies.

6 Deaths in the Phase 1 trials were examined.  
7 All deaths in Phase 2 trials were also examined except  
8 for trials in patients with advanced cancer. There  
9 were two deaths in Phase 1 trials in subjects  
10 receiving denosumab, including an accidental death and  
11 cancer progression in a breast cancer patient.

12 In the Phase 2 Dose-Finding Trial 223, there  
13 were four deaths in the denosumab group, one from a  
14 cerebrovascular accident and three neoplasms. All  
15 three neoplasms occurred in the denosumab  
16 100 milligrams Q6months cohort. In the extension  
17 phase of this dose-finding study, there was one  
18 additional death, cause unknown.

19 In the pooled osteoporosis safety database,  
20 there were 90 deaths in the placebo group and 70 in  
21 the denosumab group. The most common causes of death  
22 were neoplasms, cardiac disorders, respiratory

1 disorders and nervous system events.

2           In the pooled hormone ablation safety  
3 database, deaths were balanced across the two  
4 treatment groups. The most common causes of death  
5 were cardiac disorders, respiratory disorders, nervous  
6 system events and neoplasms. There were no imbalances  
7 in the denosumab groups in deaths in any of the  
8 Phase 3 trials.

9           In terms of serious adverse events in Trial  
10 216, which is the PMO treatment, the overall incidence  
11 of serious adverse events, which here includes fatal  
12 events, was balanced between the treatment groups.  
13 The incidence of cardiac, musculoskeletal infection  
14 and neoplasm systems were -- these events were  
15 increased in the denosumab group. In the placebo  
16 group, the incidence of serious adverse events was  
17 higher in the injury system organ class, which was  
18 driven by more fractures in this group.

19           In Trial 132, the PMO prevention trial, the  
20 denosumab group had more serious adverse events of  
21 infection and neoplasm. There were eight subjects on  
22 denosumab who developed serious infections while only



1 one placebo subject developed a serious infection.  
2 There was also an imbalance in neoplasms in this  
3 trial.

4 In both hormone ablation trials, the  
5 incidence of all serious adverse events was higher in  
6 the denosumab as compared to placebo. In Trial 135 in  
7 breast cancer patients, the denosumab group had more  
8 serious musculoskeletal and neoplasm events. In  
9 Trial 138 in prostate cancer patients, the most common  
10 serious adverse events were in the cardiac, nervous,  
11 neoplasms and infection systems. These were similar  
12 to what was observed in the PMO trials.

13 When we look at adverse events, common  
14 adverse events leading to discontinuation of  
15 investigational products in the postmenopausal trials,  
16 we see that approximately the same number of subjects  
17 in each treatment group discontinue treatment because  
18 of an adverse event. In the denosumab group, the most  
19 common adverse events there were reported as the  
20 reason for investigational product discontinuation  
21 were breast cancer, back pain and constipation. In  
22 the placebo group, lumbar and thoracic vertebral

1 fractures, breast cancer, back pain and constipation  
2 were the most common adverse terms that led to  
3 treatment discontinuation.

4           The next portion of my presentation will  
5 focus on the adverse events of special interest listed  
6 here. In some cases, these events are specific to the  
7 denosumab safety database while others are evaluated  
8 with all anti-resorptive therapies.

9           Our safety review evaluated infections.  
10 I'll present an overview of infections in each of the  
11 four primary Phase 3 trials and then focus on specific  
12 infections with imbalances between the treatment  
13 groups.

14           There were several reasons to investigate  
15 infections thoroughly. As previously mentioned,  
16 denosumab is an inhibitor of the RANK ligand. RANK  
17 and RANK ligand maybe involved in B and T cell  
18 differentiation and dendritic cell survival and may  
19 also play a role in ongoing antigen surveillance.

20           There is an early signal for infections. In  
21 Phase 1 studies, three subjects required  
22 hospitalization for pneumonia after a single dose of

1 denosumab. One of these subjects was subsequently  
2 diagnosed with lung cancer which could have  
3 contributed to the event. In the other two subjects,  
4 who were males less than 35 years old, no significant  
5 medical history was reported.

6 In Phase 2 trials in Trial 223, serious  
7 adverse events related to infection occurred in  
8 3 percent of denosumab subjects and none of the  
9 placebo or alendronate subjects.

10 The incidence of serious infections in  
11 subjects receiving denosumab was higher across all  
12 four Phase 3 primary trials in four different  
13 populations. The overall incidence of any adverse  
14 event, which would include serious and non-serious,  
15 was not higher in the denosumab group for the  
16 osteoporosis trials.

17 For the hormone ablation trials, the overall  
18 incidence of any event of infection was higher in the  
19 denosumab group. There were no imbalances in  
20 opportunistic infections between the treatment groups.

21 The main imbalance in serious events of  
22 infection is related to skin infections. Serious skin

1 infections that occurred in Trial 216 are shown here.  
2 These subjects were hospitalized for their infections.  
3 Erysipelas and cellulitis were more common in the  
4 denosumab group.

5 Trials 132 and 135 each had one denosumab  
6 subject with a serious adverse event of cellulitis  
7 while there were none in the placebo group. However,  
8 the number of serious skin infections were balanced in  
9 Trial 138 across treatment groups.

10 Additional imbalances were noted in serious  
11 ear infections and urinary tract infections. For  
12 serious ear infections in Trial 216, no placebo  
13 subjects had an event of this nature while five  
14 denosumab subjects had events coded to this event  
15 category. This included four events of labyrinthitis  
16 and one event of otitis media.

17 Serious urinary tract infections occurred in  
18 17 placebo subjects in Trial 216 and 28 denosumab  
19 subjects in Trial 216. These events were balanced in  
20 Trial 138 across the two treatments groups.

21 In Trial 216, it was noted that there were  
22 three cases of endocarditis in the denosumab group and

1 none in the placebo group. One denosumab subject died  
2 and another subject received a valve replacement.

3           Based on a 2001 article in the New England  
4 Journal of Medicine, the incidence rate of native  
5 valve endocarditis in 1.7 to 6.2 cases per 100,000  
6 person years. In this trial, in Trial 216, the  
7 exposure was approximately 11,000 person years. So  
8 the number of endocarditis cases reported in Trial 216  
9 was at least fourfold higher than would have been  
10 anticipated based on this article.

11           There were eight subjects who had adverse  
12 events coded as infective arthritis. The majority of  
13 these patients received oral antibiotics, and there  
14 were no serious events reports.

15           In summary, there was an imbalance in the  
16 number of serious infections in the denosumab group.  
17 Most notable were infections of the skin, ear and  
18 urinary tract. An imbalance in endocarditis was  
19 noted, although the event occurred rarely. An  
20 imbalance in infective arthritis was noted, although  
21 all events were non-serious. There was no evident  
22 increase in opportunistic infections.

1           New malignancies were also investigated in  
2 the denosumab primary PMO trials. Normally,  
3 pharmacology and toxicology studies in animals are  
4 conducted to evaluate carcinogenicity. However, this  
5 antibody is specific to human and nonhuman primate  
6 RANK ligand and is not active in rodents. Therefore,  
7 no carcinogenicity studies were performed due to a  
8 lack of an animal model.

9           In the Dose-Finding Trial 223, as previously  
10 mentioned, there were three deaths due to neoplasms in  
11 the 100 milligrams Q6months cohort. In this cohort,  
12 42 subjects were randomized and 41 subjects received  
13 at least one dose of denosumab. An additional  
14 observation was that breast cancer was a common  
15 adverse event leading to investigational product  
16 discontinuation in the primary PMO trials.

17           There were more new events of neoplasm in  
18 the denosumab group in the primary PMO trials. This  
19 number includes malignant, benign and unspecified  
20 conditions. When benign conditions were removed,  
21 there was a higher incidence of malignant or  
22 unspecified conditions in subjects receiving

1     denosumab.

2             What is presented here is any imbalance of  
3     0.2 percent or greater in the reported event incidence  
4     between the two treatment groups. In particular,  
5     there were more gastrointestinal, breast and  
6     reproductive malignancies in the denosumab group.  
7     However, there were more respiratory malignancies in  
8     the placebo group.

9             In summary, no carcinogenicity studies were  
10    performed due to a lack of an animal model. In the  
11    dose-finding trial, three subjects in a high dose  
12    denosumab group died of a new neoplasm. In the  
13    primary PMO studies, there was an imbalance in the  
14    incidence of malignancies in the denosumab group  
15    driven by breast, reproductive and gastrointestinal  
16    cancers. The significance of these findings is  
17    unclear.

18            Tumor progression was specifically evaluated  
19    in the breast and prostate cancer trials which  
20    enrolled subjects with non-metastatic cancer. These  
21    hormone ablation trials were not designed to evaluate  
22    cancer outcomes. However, we noted there was an

1 imbalance in metastatic events in Breast Cancer Trial  
2 135 with 4.2 percent of placebo subjects and 7 percent  
3 of denosumab subjects experiencing metastatic events.  
4 And in Trial 138, in prostate cancer subjects,  
5 5.5 percent of placebo subjects and 8.2 percent of  
6 denosumab subjects had metastatic events.

7           Our quantitative safety team noted that  
8 there was a statistically significant difference  
9 between treatment groups in the event category  
10 dermatitis and eczema and the event category rashes,  
11 eruptions and exanthems for the primary PMO trials.  
12 Based on this exploratory finding, dermatologic  
13 adverse events were investigated.

14           There was an imbalance in adverse events  
15 related to skin and soft tissue disorders. This  
16 grouping does not include skin infections. These  
17 dermatologic adverse events were not specific to the  
18 injection site. They were mainly driven by the  
19 grouping of epidermal and dermal conditions, which is  
20 the top line with 8.4 percent of placebo subjects and  
21 11 percent of denosumab subjects experiencing these  
22 events.



1           This event grouping includes several events,  
2   but the specific events that had a higher incidence in  
3   the denosumab group were dermatitis and eczema with  
4   2 percent versus 3.6 percent, pruritis with 2.4  
5   percent versus 2.7, and then rashes, eruptions and  
6   exanthems with 2.2 percent in placebo and 2.9 percent  
7   in the denosumab group.

8           Skin serious adverse events occurred in  
9   seven placebo subjects and 10 denosumab subjects in  
10   Trial 216. All these subjects were hospitalized for  
11   the event. In many of these cases, while denosumab  
12   could not be ruled out as the cause, subjects were  
13   noted to be on other medications that could also have  
14   contributed to the event. In addition, there were  
15   four cases that were categorized as -- the  
16   investigator reported it as toxic skin eruptions that  
17   were reported in Trial 216. These cases were reviewed  
18   and do not appear to be secondary to denosumab.

19           Although a subset of the skin events that  
20   were investigated had contributory factors, we  
21   continue to be concerned about the imbalance between  
22   the two treatment groups for epidermal and dermal

1 adverse events.

2           Pancreatitis was evaluated because of an  
3 imbalance in acute pancreatitis noted in Trial 216.  
4 There were a total of four placebo subjects and eight  
5 denosumab subjects in the primary PMO trials that had  
6 events of pancreatitis. There was only one subject in  
7 the placebo group with a serious adverse event while  
8 all the events in the denosumab group were serious.

9           There was no obvious temporal relationship  
10 between investigational product exposure and the  
11 development of these events and many of these cases  
12 were confounded. However, there were two noteworthy  
13 cases from the PMO primary trials that I will  
14 describe. A 74-year-old subject who had been  
15 receiving denosumab for two years developed  
16 pancreatitis 17 days after her last dose of denosumab.  
17 The investigator stated that the woman had no known  
18 risk factors for pancreatitis.

19           There was another case where a family  
20 reported that a 71-year-old subject died of acute  
21 pancreatitis in month 4 of the study. The family  
22 refused to disclose further information or provide any

1 records.

2           However, when we look at Trial 138, we see  
3 there are more cases of pancreatitis in the placebo  
4 group with four events than in denosumab subjects.  
5 Only one case was reported in denosumab. We are  
6 unclear of the significance of this imbalance noted  
7 specifically in the primary PMO trials nor of the two  
8 noteworthy cases that were previously described.

9           Because of the imbalance noted in cataracts  
10 in the prostate cancer trial, ocular adverse events  
11 were reviewed. Trial 138 enrolled men with a mean age  
12 of 75 years. Trial 216 enrolled women with a mean age  
13 of 72 years. The imbalance in cataracts was noted in  
14 Trial 138. However, this imbalance was not seen in  
15 Trial 216.

16           For Trial 138, 1.2 percent of subjects on  
17 placebo and 4.7 percent of subjects on denosumab  
18 developed cataracts. Only two of these were serious  
19 in the denosumab group. For Trial 216, 6.3 percent of  
20 placebo subjects and 5.7 percent of denosumab subjects  
21 developed cataracts. The number of these that were  
22 serious was 0.7 percent in the placebo group and

1 0.5 percent in the denosumab group.

2           It should be noted that the incidence of  
3 adverse events in the placebo group for Trial 138 was  
4 lower than the incidence seen in Trial 216. There was  
5 no notable imbalance between treatment arms in other  
6 ocular adverse events that were reviewed.

7           The significance of this imbalance in the  
8 incidence of cataracts in Trial 138 is unclear at this  
9 time. As mentioned, the sponsor has proposed a  
10 randomized placebo-controlled clinical trial to  
11 evaluate the risk of cataracts in men with prostate  
12 cancer receiving androgen deprivation therapy.

13           Cardiovascular adverse events are common in  
14 the age groups enrolled in the denosumab trials and  
15 were thoroughly evaluated. Osteoprotegerin is a  
16 cytokine and a TNF receptor superfamily. Its main  
17 function is inhibition of the RANK ligand and  
18 osteoclast differentiation. Literature reports  
19 suggest an association between osteoprotegerin levels  
20 and arterial wall calcification, cardiovascular  
21 disease and mortality. There is a theoretical  
22 potential for elevated osteoprotegerin levels with

1 denosumab inactivation of RANK ligand as it binds to  
2 the same target.

3           There was a specific evaluation of cardiac  
4 events which included the following: death and  
5 cardiovascular serious adverse events from Studies 216  
6 and 138 were adjudicated by an independent panel of  
7 cardiologists that were assembled by the sponsor.  
8 There was a similar incidence of cardiac deaths and  
9 serious adverse events that were positively  
10 adjudicated in the treatments arms.

11           Osteoprotegerin levels were measured in a  
12 substudy of Trial 216. Osteoprotegerin levels did not  
13 increase with denosumab use. Abdominal aortic  
14 calcification scores were assessed using the x-rays  
15 that had been collected for fracture analyses. No  
16 differences in abdominal aortic calcification scores  
17 were seen. Therefore, while the methods used to  
18 assess cardiovascular safety do have limitations,  
19 there's no clear cardiovascular safety signal based on  
20 the available data.

21           Hypocalcemia is an event that's closely  
22 evaluated with all anti-resorptive therapies.

1 Hypocalcemia occurs with the anti-resorptive therapy  
2 because these therapies essentially function to shut  
3 off bone as a reservoir for calcium. All subjects in  
4 the primary Phase 3 trials were supplemented with  
5 calcium and Vitamin D. Timing of the calcium  
6 measurements in these primary Phase 3 trials was at  
7 one month, which missed the anticipated calcium nadir  
8 which is eight to 11 days post-dose.

9           One denosumab treated subject in Trial 138  
10 reported a serious event of hypocalcemia. In the  
11 Phase 3 PMO trials, 1.6 percent of subjects had an  
12 asymptomatic corrected calcium level less than 8.5.  
13 Corrected calcium levels less than 7.5 were rare.

14           Osteonecrosis of the jaw is an adverse event  
15 of interest for all anti-resorptive therapies.  
16 osteonecrosis of the jaw may be associated with  
17 inhibition of bone remodeling. Potential cases of ONJ  
18 were adjudicated by an independent committee assembled  
19 by the sponsor. There were pre-specified search  
20 criteria to identify potential cases of osteonecrosis  
21 of the jaw.

22           There was a balanced distribution of these

1 potential cases that were sent to the committee for  
2 adjudication. No cases met the definition of ONJ.  
3 Cases of ONJ, however, are being reported in denosumab  
4 subjects in ongoing and completed advanced cancer  
5 trials.

6 Immunogenicity is the last topic that I'll  
7 be presenting. Therapeutic proteins have the  
8 potential to elicit an immune response. A three-step  
9 process for detection of antibodies to denosumab was  
10 used, a screening immunoassay to detect binding  
11 antibodies, a second immunoassay to confirm binding  
12 antibodies and a cell-based bioassay to evaluate for  
13 the presence of neutralizing antibodies. Most  
14 clinical studies from the denosumab program had  
15 evaluations of immunogenicity.

16 Binding antibodies to denosumab were  
17 measured in subjects with postmenopausal osteoporosis,  
18 cancer and other conditions such as rheumatoid  
19 arthritis. In these subjects exposed denosumab, the  
20 presence of pre-existing binding antibodies was  
21 identified in 0.1 percent to 0.5 percent of subjects  
22 while 0.5 percent to 1.1 percent had binding

1     antibodies according to these assays used.

2                 When the placebo and active control subjects  
3     were looked at, 0.2 percent of these had binding  
4     antibodies present, pre-existing binding antibodies  
5     were present, while 0.3 percent were identified later.  
6     These subjects were never exposed to denosumab. The  
7     significance of these binding antibody assays is  
8     unclear at this time.

9                 The last speaker for the FDA this morning is  
10    Dr. Theresa Kehoe.

11                DR. KEHOE: Thank you. I'll be presenting  
12    the findings for the bone histomorphometry studies and  
13    then will provide a summary of the denosumab safety,  
14    and then conclude with a discussion of FDA's risk  
15    benefit assessment.

16                Evaluation of bone biopsy specimens is a  
17    required safety evaluation for agents seeking a  
18    treatment of osteoporosis indication. Two types of  
19    evaluations occur on these bone biopsy specimens. one  
20    is to evaluate for evidence of pathologic histology  
21    and the second is quantitative histomorphometry, which  
22    allows for tissue level assessment of bone turnover



1 and bone mineralization.

2           Abnormalities of bone mineralization has  
3 been a focus with bisphosphonate drugs as these drugs  
4 are incorporated into the pyrophosphate crystals when  
5 bone is mineralized.

6           When we talk about bone histology, recall  
7 from the slide presented by Dr. Stehman-Breen earlier  
8 this morning that there are two types of bones. First  
9 you see trabecular or cancellous bone, which is the  
10 sponge-like bone in the contact with the marrow space.  
11 It is metabolically active and rapidly turned over.  
12 Cortical or compact bone is the denser or outer  
13 envelope of bones, and it's found on all bones.

14           In general, the bone biopsy specimens  
15 revealed normal lamellar bone and normal bone  
16 mineralization. The following abnormalities were  
17 noted. Five subjects in Trial 216 did not have  
18 osteoid that could be visualized at month 24. Osteoid  
19 is unmineralized new bone matrix. This may be  
20 evidence of over suppression of bone turnover such  
21 that no new bone is being formed.

22           One subject in Trial 216 had normal

1 histology at month 24 but had developed endosteal  
2 resorption of cortical bone at month 36. Endosteal  
3 resorption of cortical bone or increased bone  
4 resorption on the inside surface of cortical bone,  
5 this finding can be associated with reduced bone  
6 strength. In addition, one subject maintained on  
7 alendronate in Trial 234 had evidence of marrow  
8 fibrosis.

9           Quantitative histomorphometry evaluation  
10 requires labeling the bone to enable measurements of  
11 bone resorption and bone formation. Because it is  
12 taken up by newly mineralized bone and fluoresces  
13 under polarized light, tetracycline or its congeners  
14 are used to label bone. In this discussion, the  
15 agents, whether tetracycline or demeclocycline, used  
16 to label bone are referred to as tetracycline.

17           Subjects in the bone biopsy substudies  
18 received two timed spaced courses of tetracycline.  
19 The presence of two lines of labeling or tetracycline  
20 double label provides evidence of active bone  
21 remodeling and formation. Trabecular double label is  
22 necessary to full assess quantitative histomorphometry

1 parameters. If double tetracycline labeling is not  
2 seen on the trabecular bone in the measurement field,  
3 then an extended label search can be conducted and  
4 includes a search for single or double tetracycline  
5 labeling in all of the trabecular and cortical bone  
6 fields.

7           Outlined in this table are the results from  
8 the extended label search for the bone biopsy samples  
9 from Study 234, which is the bisphosphonate switch  
10 study, and Trial 216, the postmenopausal fracture  
11 study. The first row shows the number of biopsy  
12 samples that were obtained in these studies, month 12  
13 for Study 234 and both month 24 and 36 for Study 216.

14           All samples obtained from placebo and  
15 alendronate subjects had either -- they had label  
16 present that was either single label or double label  
17 on the extended label search. However, for biopsy  
18 samples obtained from subjects transitioning from  
19 alendronate to denosumab in Study 234, 20 percent had  
20 no label at month 12. In Trial 216, no label was  
21 present in 35 percent of the biopsy specimens obtained  
22 at month 24 and 38 percent of the biopsy specimens

1     obtained in month 36.

2                 Full evaluation of all static and dynamic  
3     histomorphometry parameters require the presence of  
4     double tetracycline labeling in the histomorphometry  
5     measurement field. Any label and no label rows at  
6     this table show the presence of any label seen on  
7     extended label search or anywhere in that bone biopsy.  
8     The last line, the full evaluation row here, shows the  
9     number of samples that had double tetracycline label  
10    in the trabecular measurement field and were available  
11    for full assessment of bone histomorphometry  
12    parameters.

13                What we can see in this last row is that a  
14    full evaluation was possible for all biopsy specimens  
15    from alendronate-treated subjects and 40 percent of  
16    denosumab-treated subjects in Trial 234 at month 12.  
17    In Trial 216, a full evaluation was possible in  
18    84 percent of subjects who received placebo at  
19    month 12 and 16 percent of subjects who received  
20    denosumab at month 24. In Trial 216 at month 36,  
21    88 percent of placebo subjects and 10 percent of  
22    denosumab treated subjects had the availability of

1 having a full assessment of bone histomorphometry.

2           One question that may be asked is how does  
3 this compare to other agents that have previously been  
4 reviewed for the same indications. In those samples,  
5 the rate of fully evaluable bone biopsies is 50  
6 percent of higher.

7           The results of the quantitative  
8 histomorphometry parameters are outlined in the  
9 briefing document. In Trial 216, at month 24 and 36,  
10 parameters of bone resorption were significantly  
11 decreased. In some evaluable bone biopsy specimens,  
12 remodeling activity was virtually absent at month 36.  
13 There was no evidence of a mineralization defect with  
14 denosumab-treated subjects. In the patients  
15 previously treated with alendronate, bone resorption  
16 parameters were further suppressed with denosumab  
17 therapy when compared with continued alendronate  
18 therapy.

19           The absence of tetracycline label may be an  
20 indication of very low bone remodeling and possibly  
21 even over suppression of bone turnover. As previously  
22 discussed by Dr. Popat, a large number of subjects in

1 Trial 216 had suppression of bone resorption marker  
2 CTX to the point where levels were undetectable. In  
3 order to further evaluate whether the lack of  
4 tetracycline label seen in the bone biopsy samples  
5 could be related to suppression of bone turnover seen  
6 with CTX levels, we questioned whether those subjects  
7 with no trabecular label also had undetectable levels  
8 of CTX at the month 1 time point.

9           This table shows that the biopsy samples  
10 from Trial 216 that had no label or double  
11 tetracycline present and whether these patients had  
12 undetectable levels of CTX or detectable levels of  
13 CTX.

14           As outlined, in patients with biopsy samples  
15 that had no detectable tetracycline label, month 1 CTX  
16 levels were also undetectable in 87 percent of  
17 denosumab-treated subjects at month 24 and 75 percent  
18 of subjects treated with denosumab at month 36; while  
19 patients with biopsy samples that had double label  
20 present, 100 of placebo subjects in both time points  
21 also had detectable levels of CTX and 67 percent of  
22 denosumab subjects had detectable levels of CTX.

1           As previously discussed, bone formation and  
2 bone resorption are tightly couple processes. With  
3 regard to the bone formation market P1NP, seven  
4 subjects who had bone biopsies had P1NP levels that  
5 were undetectable at month 12. That was the earliest  
6 time point P1NP was evaluated. All of those subjects  
7 were treated with denosumab, and six of those subjects  
8 had no tetracycline labeling on their bone biopsy  
9 specimens.

10           So in summary, based on the bone  
11 histomorphometry analysis, treatment with denosumab  
12 decreases bone resorption as evidenced by the  
13 suppression of bone histomorphometry parameters. Bone  
14 resorption and bone formation are tightly coupled  
15 processes, and treatment with denosumab also decreases  
16 bone formation or overall bone turnover.

17           One of the reasons we are concerned over the  
18 over suppression of bone turnover is the 2004 paper by  
19 Odvina, et al., that presented nine patients who  
20 sustained non-spine fractures while on bisphosphonate  
21 therapy. Some also had delayed or absent fracture  
22 healing. Bone histomorphometry from biopsy specimens

1 revealed absence of double tetracycline labeling as  
2 well as absent or reduced single tetracycline labeling  
3 in all patients.

4           So to summarize, the denosumab safety  
5 evaluation, overall when evaluating the denosumab  
6 safety database, the number of deaths was not higher  
7 with denosumab therapy. There was an imbalance in  
8 serious adverse events with denosumab use primarily by  
9 cardiac, musculoskeletal disorders and infections.

10           The adverse events of greatest concern are  
11 infections, new malignancies in the postmenopausal  
12 osteoporosis population, tumor progression in the  
13 breast and prostate cancer hormone ablation population  
14 and the dermatologic adverse events.

15           Data from the histomorphometry evaluation  
16 suggests that CTX -- from the evaluation of both CTX  
17 and histomorphometry suggest a possible over  
18 suppression of bone turnover. However, the long-term  
19 consequences of these findings are not clear.

20           To begin the summary of the risk benefit  
21 assessment of denosumab, I want to first present what  
22 the agency's interpretation of the populations of



1 patients that these indications are intended for. For  
2 the treatment of postmenopausal osteoporosis, the  
3 indication encompasses all patients who osteoporosis  
4 diagnosed by BMD or a history of a low trauma  
5 fracture. While we have not included the FRAX  
6 calculator as an inclusion criteria in the design of  
7 Phase 3 osteoporosis trials, we do believe that the  
8 treatment of postmenopausal osteoporosis indication  
9 also encompasses patients who are at increased risk  
10 for fracture based on the FRAX calculator.

11           The prevention of postmenopausal  
12 osteoporosis indication would include patients with  
13 low bone mass who are not considered at increased risk  
14 for fracture based on the FRAX calculator. The  
15 treatment of bone loss in patients undergoing hormone  
16 ablation for breast or prostate cancer, the indication  
17 would include patients who have evidence of  
18 osteoporosis diagnosed by the same criteria used for  
19 treatment of postmenopausal osteoporosis as well as  
20 those who have been on hormone ablation therapy and  
21 are demonstrating significant bone loss.

22           The prevention of bone loss in patients

1     undergoing hormone ablation for breast or prostate  
2     cancer, the indication will include patients with  
3     normal bone mineral density or low bone mineral  
4     density who do not have a significant bone loss with  
5     hormone ablation therapy or have newly begun hormone  
6     ablation therapy.

7             As shown in this slide, the agency's  
8     interpretation aligns with the currently published  
9     treatment guidelines for postmenopausal osteoporosis  
10    as previously reviewed by Dr. Siris. The National  
11    Osteoporosis Foundation recommends BMD testing for  
12    women over the age of 50 and initiation of therapy for  
13    those with a history of fracture, a BMD T score less  
14    than minus 2.5 or an increased ten-year fracture risk  
15    based on FRAX.

16            In the breast cancer population, the  
17    American Society of Clinical Oncology currently  
18    recommends BMD testing for all women on aromatase  
19    inhibitors and initiation of therapy for those with a  
20    T score of less than minus 2.5. For patients with low  
21    bone mass, yearly monitoring of BMD is recommended.

22            In the prostate cancer population, there are

1 no guidelines from major organizations. However,  
2 several reviews in working groups are available in the  
3 literature, including one from the North American  
4 Symposium published in Cancer in 2004. They recommend  
5 guidelines similar to those for breast cancer on  
6 aromatase inhibitor.

7           So in summary, denosumab is effective in  
8 reducing the incidence of fractures in postmenopausal  
9 osteoporotic population. Denosumab is also effective  
10 in increasing bone mineral density in postmenopausal  
11 women with low bone mass, in women undergoing  
12 aromatase inhibitor therapy for breast cancer, and in  
13 men undergoing androgen deprivation therapy for  
14 prostate cancer.

15           Neither of the primary trials evaluating  
16 denosumab in the hormone ablation population contained  
17 pre-specified plans to identify detrimental effects on  
18 cancer outcomes such as progression free survival or  
19 overall survival. Overall survival was an exploratory  
20 endpoint in both the breast and prostate cancer bone  
21 loss trials. However, given the eligible population  
22 for enrollment included subjects with non-metastatic

1 disease, few events would be anticipated.

2           In both the breast cancer hormone ablation  
3 trial and the prostate cancer hormone ablation trial,  
4 an insufficient number of events occurred and it is  
5 not possible to make any definitive statements  
6 regarding overall survival.

7           Safety concerns remain. These include the  
8 imbalance of infections; serious adverse events; most  
9 notably of the skin, ear and urinary tract; imbalance  
10 of endocarditis. While the event rates are low, they  
11 do exceed the background rate expected. The imbalance  
12 of infective arthritis, the imbalance of new  
13 malignancies in the postmenopausal osteoporosis  
14 population, the imbalance of tumor metastases in the  
15 cancer bone loss trial population, and the imbalance  
16 of dermatologic adverse events, most notably  
17 dermatitis events that were statistically  
18 significantly higher in those receiving denosumab.

19           One remaining question is whether denosumab  
20 reduces bone resorption and bone formation to the  
21 point that we need to be concerned regarding over  
22 suppression of bone turnover. In the denosumab

1 program, we have discussed the evidence of significant  
2 suppression of the bone resorption marker CTX. The  
3 bone formation marker P1NP follows CTX and is also  
4 significantly suppressed.

5           When we combine this evidence with the bone  
6 histomorphometry findings, the concern remains the  
7 potential for long-term consequences of this degree of  
8 suppression of bone resorption and bone formation.  
9 Unfortunately, the state of the science for both  
10 markers of bone turnover and bone histomorphometry are  
11 such that it is not possible to predict long-term  
12 outcomes based on the data that we have. We can only  
13 say that they are unclear.

14           Another finding that may offer some  
15 suggestion of a potential for long-term consequences  
16 would be the hip fracture findings in year 3 of Study  
17 216. The incidence of hip fractures increased  
18 compared to year 2 and was the same as placebo.

19           We welcome the committee's discussion on  
20 these findings as well as our consideration of our  
21 questions later this afternoon. And in closing, I  
22 would like to take the opportunity to acknowledge all

1 the members of the FDA review team who worked on this  
2 application and I apologize to anybody that I've  
3 inadvertently left off the slide. Thank you.

4 DR. CARSON: Thank you, members of the FDA  
5 staff for highlighting these points that you brought  
6 up.

7 We'll have now questions from the panel to  
8 all the presenters this morning. There is a lot of  
9 information we received on requests for four different  
10 applications on a variety of populations. I thought  
11 about how we could organize questions and then decided  
12 there was really no way to. So let me ask, though,  
13 just in the convenience, Dr. Eisenberg, if maybe you  
14 want to take the -- in bringing up anyone who you  
15 think most will be able to answer questions and then  
16 you can call from your group.

17 DR. EISENBERG: Sure.

18 DR. CARSON: So let me open it to the  
19 committee.

20 Yes, Dr. Mortimer.

21 DR. MORTIMER: I wonder if you could  
22 summarize the characteristics of the breast cancer

1 population for the 20 in the postmenopausal  
2 osteoporosis studies, the 20 compared to the 10. I  
3 mean, were there characteristics in age? Were older  
4 women more likely to develop --

5 DR. EISENBERG: Let me understand the  
6 question. When you say the cases of breast cancer  
7 that occurred?

8 DR. MORTIMER: Correct.

9 DR. EISENBERG: Okay.

10 DR. MORTIMER: What was the phenotype of the  
11 disease and what were the risk factors of the  
12 patients?

13 DR. EISENBERG: Sure. I think Dr. Roger  
14 Dansey, who was responsible for those programs, would  
15 be best able to respond to that.

16 DR. DANSEY: Good morning. As you saw in  
17 the initial presentation, just perhaps to orient you  
18 to how we evaluated breast cancer in the 216 study,  
19 what you're looking at is the overall population of  
20 women who developed breast cancer on studies, on the  
21 left part of the slide are the new diagnoses. And you  
22 can see there are 26 subjects on placebo, 28 on

1    denosumab. And for those subjects with a prior  
2    history of breast cancer, we have two on placebo and  
3    six on denosumab.

4           And in terms of the disease characteristics,  
5    which I think what you were asking, if we look at the  
6    stage distribution, for example, in the newly  
7    diagnosed, it's 16 Stage 0, 1 or 2 in placebo, 19 with  
8    denosumab. For the Stage 3 or 4, it's 4 and 5  
9    unknown, 6 and 4 no status as you can see, 10 known  
10   positive, 9 known positive with denosumab and so on.

11           Histologically, there were three in situ  
12   cancers -- I'm sorry; three in situ cancers on  
13   denosumab, and the invasive groups were balanced.

14           We also did look at age. And there were no  
15   specific characteristics that I think we could  
16   identify clinically that would suggest any difference.  
17   And as I've pointed out, the numbers are similar.

18           DR. MORTIMER: Do you have a slide of the 20  
19   and 10 from the PMO trials?

20           DR. EISENBERG: The 20 and 10 refer to  
21   discontinuations and they're distributed. I think  
22   Dr. Dansey can provide some background, but there's no



1   apparent relationship between discontinuation that  
2   Dr. Stehman-Breen commented in those studies and any  
3   of the background features. It appears simply to be a  
4   difference in whether they were in denosumab or  
5   placebo. There's no difference in the patients. I  
6   don't know.

7               Dr. Dansey, do you want to comment further?  
8   We did a pretty thorough analysis. It's simply  
9   discontinuation. These are all the cancers in that  
10  study.

11              Now, in the HALT study, did you want  
12  information on that one as well? There were new  
13  cancers in the HALT study. But Dr. Dansey can comment  
14  on that, in the breast cancer HALT experience, if you  
15  want to make comments.

16              DR. DANSEY: So perhaps just to reiterate  
17  what you said about the discontinuations. There was  
18  no protocol specified requirement for discontinuation.  
19  So local factors, which we assume are multifactorial,  
20  access to care and so on, likely would have applied.  
21  From the breast cancer point of view, the progression  
22  of disease, which was mentioned earlier, we've also

1 performed a very careful review of that information in  
2 the breast cancer HALT patient population.

3           And we see in the treatment period, three  
4 subjects on placebo with clear evidence of metastatic  
5 disease, four subjects on denosumab with clear  
6 evidence of metastatic disease. And so the treatment  
7 period of two years, you can see there -- and this is  
8 based on review of verbatim terms. And when we look  
9 at the off treatment phase, which is now subjects in  
10 follow up, we see two subjects with clear evidence of  
11 disease progression and two subjects on placebo.

12           And I would point out the 120 day -- the  
13 follow-up period is about to complete, and we'll have  
14 full data for that in the near future.

15           DR. EISENBERG: Two-year follow-up data.

16           DR. DANSEY: Two-year follow-up.

17           DR. CARSON: Dr. Emerson?

18           DR. EMERSON: I guess I have a question  
19 going back to the very beginning where Dr. Siris was  
20 talking about the impact and was talking about what  
21 populations should be treated. So particularly slides  
22 10 and 12 was what I'm interested in.

1 DR. EISENBERG: Dr. Siris is working her way  
2 over the microphone and is probably best able to  
3 respond.

4 DR. SIRIS: It would be awkward if I fell  
5 and broke something trying to get to the microphone.

6 Could we have those slides up, please?

7 DR. EMERSON: So you're talking about the  
8 number of women with fractures versus the proportions  
9 of women within those groups.

10 Have you looked at the number needed to  
11 treat? I mean the concept that even though there's  
12 the large number of fractures among the negative 1.5  
13 to negative 2.0 to sort of look at the extreme value,  
14 that with only 15 fractures per 1,000 person years,  
15 how many subjects would you need to treat to prevent  
16 one there as opposed to the right-hand side of that?

17 DR. SIRIS: That was not a purpose of the  
18 NORA study. The NORA study was not trying to tell  
19 anybody when to treat. The NORA study was able to  
20 show, because we had this very large population, that  
21 while the rates of fracture were highest in those with  
22 the lowest BMDs at baseline, which is what you would

1 predict from what the T score tells you, if you were  
2 to ignore the women with osteopenic T scores, you  
3 would miss about 52 percent of the women who actually  
4 fractured.

5           The take-home message there was we have to  
6 be able to risk stratify women with osteopenia in  
7 order to identify those osteopenic women at higher  
8 risk and those osteopenic women at lower risk. And  
9 one of the important risk factors in conjunction with  
10 osteopenia, for example, would be age. So an older  
11 osteopenic woman who's presumably had many more years  
12 to lose bone may have the same bone density as a  
13 younger osteopenic woman but the older woman's bone  
14 quality may be much worse. And by virtue of her age,  
15 she may have co-morbidities to make her more likely to  
16 fall, et cetera.

17           And the FRAX algorithm allows you to look at  
18 a series of risk factors in conjunction with the  
19 osteopenic T score to identify the higher risk patient  
20 in whom treatment would be appropriate and to identify  
21 the lower risk osteopenic whom you would not recommend  
22 for treatment.

1 DR. EMERSON: So then that leads to  
2 slide 12, which is the FRAX algorithm.

3 DR. SIRIS: Slide 12 was an example of the  
4 use of the algorithm in a patient who is 67 years of  
5 age, has a T score of minus 2.1 at the femoral neck.  
6 And this would define her as being osteopenic. When  
7 you analyze your risk factor profile, you see the list  
8 of risk factors under FRAX include -- yes.

9 DR. EMERSON: So one of the ones that I'd  
10 like to focus on in particular on this -- because  
11 we're going to a 10-year predictive range.

12 DR. SIRIS: Yes.

13 DR. EMERSON: And whenever you get into that  
14 game, if you take a newborn baby boy and predict risk  
15 of prostate cancer over 80 years, it's exceedingly  
16 high but we would not want to start preventive therapy  
17 or treatment at that age.

18 So we've got a 10-year predictive value and  
19 we've also got such risk factors as para fractured  
20 hip, so that's clearly just a sort of baseline risk  
21 factor, a family history and things like this.

22 What's known about the three-year history

1     that we've actually tested in this trial?  What's that  
2     risk and how that relates?

3             DR. SIRIS:  Well, FRAX gives you a 10-year  
4     risk which is the way FRAX was set up.  The risk  
5     factors in FRAX were chosen because they are largely  
6     independent of bone mineral density, not 100 percent  
7     independent, but many of them are significantly  
8     independent of bone mineral density.  They're  
9     showing --

10            DR. EMERSON:  But my question here is, is  
11     this predicting people who will eventually develop  
12     disease or is this predicting people who have some  
13     clinical disease that will be rapidly progressive.  
14     And by the time we're looking at --

15            DR. SIRIS:  I don't think it tells you any  
16     of those things.  I don't think it works that way in  
17     osteoporosis.  I think the concept that osteopenia is  
18     a precursor to osteoporosis is a somewhat outmoded  
19     concept.  I think the point is that women after  
20     menopause lose bone.  Women after menopause have a  
21     variety of risk factors that they may or may not have  
22     and that we now have a better of way of identifying

1   those patients at high risk for fracture than simply  
2   looking at a BMD, which is the way we did it since  
3   about 1994. And those individuals -- could I have the  
4   next slide up, please?

5               DR. EMERSON: Just to clarify. One of the  
6   big question is we've got two different indications.  
7   One is treatment.

8               DR. SIRIS: Yes.

9               DR. EMERSON: And we have 8,000 women  
10   treated under that. The other is prevention, and we  
11   have 300 women treated under that. And the concept of  
12   as we're looking for this, it will be very much  
13   concern to say how early should we start treatment.  
14   And looking at something like FRAX and looking at the  
15   risk factors, it's certainly of a time range that we  
16   might worry that it's not necessary to start  
17   prevention yet.

18              DR. SIRIS: I think that's really an  
19   excellent question, and I think that the point is  
20   that, traditionally, prevention has been the  
21   prevention of bone loss. Treatment has been treatment  
22   of the disease in which fracture risk is elevated and,

1     therefore, you want to intervene to lower the risk of  
2     fractures. And I believe that's a throwback to the  
3     estrogen era when we knew that estrogen prevented bone  
4     loss and that women with estrogen appeared to have  
5     fewer fractures than women not getting estrogen. But  
6     that's an older concept.

7             It became clear -- and I think the NORA data  
8     was one of many studies that have documented this,  
9     that osteopenia is a risk factor. It's not a disease.  
10    It's a lowness of bone mineral density which in  
11    association with other risk factors can promote a  
12    fracture risk as high as simply having a T score of  
13    minus 2.5 depending on this combination. And the FRAX  
14    algorithm allows you to identify those people.

15            Now, it was interesting to hear what you  
16    said, Dr. Kehoe, that you consider a high FRAX score a  
17    treatment indication, which I would interpret as  
18    saying that if someone were osteopenic and their FRAX  
19    showed that they were at very high risk for fracture  
20    because of the other risk factors, that they would  
21    qualify for treatment under the treatment indication.  
22    Right now, third-party payers will not cover an



1 osteopenic woman because that's the only diagnosis you  
2 can give is osteopenia. A FRAX score is not a  
3 diagnostic category.

4           So we're going to be caught in a situation  
5 where we're going to have to redefine some things in  
6 order to assure that women, in fact, can get  
7 medication if it's deemed appropriate and also that it  
8 can be reimbursed. That's kind of an aside.

9           DR. CARSON: Excuse me. I'm sorry. We have  
10 a number of questions ready. And we do have time set  
11 for discussion, and I'd like to just limit this to  
12 questions about the presentations rather than  
13 discussion.

14           DR. SIRIS: Thank you.

15           DR. CARSON: Dr. Buzdar?

16           DR. BUZDAR: I have two questions. One was  
17 that it was brought up that these drugs, that this  
18 antibody can be given safely to patients who have  
19 abnormal renal function. But I did not see, maybe I  
20 missed it, what fraction of patient population in  
21 these study had abnormal renal function and was it  
22 changed or did it remain stable?

1           The other question which I have is about  
2 breast cancer, that there was 10 versus 20 new breast  
3 cancer diagnosed in the placebo versus the treatment.

4           In the patient population, did they estimate  
5 by using some of the models like Gail model or things  
6 like that, like what was the predictive probability of  
7 developing new breast cancer in the time frame which  
8 the patients were observed.

9           Is it above it, is it below it, or is it  
10 within the same range?

11           DR. EISENBERG: First, just to clarify your  
12 second question, then I'll ask Dr. Stehman-Breen. I  
13 think we responded to this -- to Dr. Mortimer's  
14 question.

15           There were 10 versus 20 refers to  
16 discontinuations in the clinical trial. The data we  
17 showed were actually 26 and 28 new breast cancers  
18 between denosumab and placebo. So that's the data in  
19 terms of new breast cancers in the trial. And I'll  
20 ask Dr. Stehman-Breen to comment on --

21           Dr. Mortimer, is it okay?

22           We'll finish the first question then.

1           So there were additional studies that were  
2   done in at-risk populations in terms of renal failure,  
3   and I'll ask Dr. Stehman-Breen just to comment on that  
4   briefly.

5           DR. STEHMAN-BREEN:   So as I mentioned in my  
6   presentation, we didn't exclude women in the fracture  
7   study based on level of renal function, and about half  
8   the women had estimated glomerular filtration rates  
9   that were below 50 percent.   So we actually had quite  
10   a bit of data with regard to the safety and efficacy  
11   in that population.   The efficacy is identical to that  
12   seen in the larger population in those with various  
13   levels with renal function, and I'm happy to show you  
14   to that if you're interested.

15           In addition, you asked about whether there  
16   was any evidence of progression of renal disease.  
17   Denosumab is not renally cleared, and so it doesn't  
18   cause acute renal failure like bisphosphonates can.  
19   There was no evidence of differences in renal  
20   function.   That was true with denosumab versus placebo  
21   in either our large PMO fracture study or a smaller  
22   dedicated study in renal dysfunction.

1 DR. EISENBERG: Any predictive factors in  
2 the clinical trial in the women who did have breast  
3 cancer? I don't think we saw anything that was  
4 predictive.

5 DR. BREHMAN-STEEN: No.

6 So perhaps we should go ahead and repeat the  
7 second question with regard to breast cancer so  
8 everybody can refresh their --

9 DR. BUZBAR: The second question was that  
10 you have two large subgroups treated with placebo and  
11 treated with your antibody. The question is that you  
12 can use a Gail model or some similar model to see that  
13 in the study period what will be the predictive  
14 probability of developing breast cancer in that  
15 period. Was that number above or below the threshold  
16 which it would --

17 DR. BREHMAN-STEEN: So let me first again  
18 clarify and perhaps if we can bring the slide up with  
19 regard to breast cancer from the core deck. We had a  
20 similar rate of new breast cancers diagnosed in our  
21 large PMO treatment study. What was different between  
22 the groups -- as you can see there were 26 in the

1 placebo group and 28 in the denosumab group. So  
2 that's a very important point.

3           What was different was the number of  
4 discontinuations due to adverse events of breast  
5 cancer, 20 in the denosumab group, 10 in the placebo  
6 group. And again, as we presented in the  
7 presentation, when we looked at these various  
8 prognostic indicators that you can see on the slide,  
9 there didn't appear to be a difference between those  
10 treated with denosumab or those treated with placebo  
11 that would differentiate the phenotype for the breast  
12 cancers.

13           I think Dr. Mortimer, you have a question.

14           DR. CARSON: Yes, but she's in line.

15           DR. EISENBERG: Just to complete the answer,  
16 if one looks at predictive rates, just at the  
17 background rate in this population based on  
18 standardized incident ratios for what we've observed,  
19 in this trial it would be .7 percent. It would be .7  
20 versus the predicted rate. So it would be lower  
21 overall.

22           DR. CARSON: Does that answer your question?

1           Okay.

2           Dr. Johnson?

3           DR. JOHNSON: Yes, I'd like to start off by  
4    thanking all the speakers. The presentations were  
5    excellent and very useful in adding to our knowledge  
6    about this medication.

7           My main question is related to the  
8    possibility of immunosuppression. I know that you  
9    stated that you're continuing the seven-year expansion  
10   of the PMO trial and also four- and two-year  
11   extensions of the HALT trials.

12          Can you give us any further information,  
13   particularly related to risk of infection? Because  
14   that appeared to be a fairly consistent finding also  
15   in terms of dermatologic abnormalities. So do you  
16   have any data from any of the extensions that you can  
17   enlighten us on the risks of immunosuppression?

18          DR. EISENBERG: Dr. Stehman-Breen will  
19   comment.

20          DR. STEHMAN-BREEN: Yes, as you mentioned,  
21   the PMO fracture study has a large extension study  
22   that's ongoing. The study has been ongoing for a

1 little over a year. And as I mentioned, it's  
2 open-label, single-arm study. So we don't have a  
3 comparison group. But in the limited amount of data  
4 that we've been able to observe to date, we haven't  
5 seen any unexpected infections such as an unexpected  
6 higher rate of opportunistic infections.

7 Did that answer your question?

8 DR. JOHNSON: I know that, though, with the  
9 original study you didn't see an increase in  
10 opportunistic increase infections, but you saw an  
11 overall increased risk of infections.

12 Have you looked at that compared to the  
13 original study in terms of the risk?

14 DR. STEHMAN-BREEN: Again, we have  
15 relatively limited data to date, but we haven't  
16 observed a higher risk of serious adverse events of  
17 infection in the extension study to date. But we'll  
18 be, of course, to continuing to monitor to this as  
19 more of this data becomes available.

20 DR. CARSON: Dr. Margolis?

21 DR. MARGOLIS: Thank you. I have two  
22 somewhat unrelated questions, although one's directly

1 to the question that was just brought up.

2           There were many speakers who spoke about the  
3 increased risk of skin infections, serious adverse  
4 events, and they were listed as three different  
5 categories but just lumping them for a second. One of  
6 the speakers also mentioned that it could be because  
7 of local skin increased inflammation, and one also  
8 implied that there may have been only the lower  
9 extremity and could be related to venous disease.

10           So I was just wondering if you could talk a  
11 little bit more about these. Did they receive IV  
12 antibiotics? Did they have increased white counts,  
13 fevers? Were they recurrent? Were they related, much  
14 higher in people with venous disease? That was the  
15 first question.

16           Then the second had to do with the secondary  
17 analysis done by the FDA on Study 216 looking at hip  
18 fractures and claiming that by the third year the risk  
19 was about the same in the two groups. I guess my  
20 question is for those individuals who had hip  
21 fractures, were they maintained in the study or were  
22 actually the risks of the population, did that change



1 over time? And what is the likelihood of somebody  
2 having a second hip fracture if, in fact, those people  
3 were to maintain in this study? Thank you.

4 DR. STEHMAN-BREEN: So let me first address  
5 your question with regard to infection. It is a nodal  
6 finding that we saw an overall balance of skin  
7 infections adverse events but there is a higher risk  
8 of serious adverse events in skin infection.

9 Now, with regard to the characteristics,  
10 this illustrates across the program some important  
11 characteristics of the patients that developed  
12 cellulitis or erysipelas, serious adverse events of  
13 cellulitis and erysipelas. You can see the mean age  
14 was 79 in the placebo group and 74 on the denosumab  
15 group. The number of days from the last dose of study  
16 drug was similar between the two groups. The level of  
17 severity was generally similar between those in the  
18 placebo group and those in the denosumab group. Of  
19 note, there was one fatal adverse event of cellulitis  
20 in a subject who was quite complicated and had a very  
21 advanced pancreatic cancer that had invaded into the  
22 ventricle.

1           You can see that the vast majority of these  
2   were lower extremity infection, 100 percent in the  
3   placebo group, 88 in the denosumab group. And again,  
4   about half of them had risk factors for skin  
5   infections. Most as would be expected because they  
6   were hospitalized received IV antibiotics. But none  
7   of them discontinued due to the serious adverse event.  
8   And it's notable that there was only one occurrence in  
9   each group despite in the denosumab group continued  
10  exposure to denosumab.

11           DR. CARSON: Dr. Rosen?

12           DR. ROSEN: (Off mic)

13           DR. STEHMAN-BREEN: They had very typical  
14  courses. Not all of them actually had fevers and  
15  chills. The majority of them actually had -- about 15  
16  percent had fevers. About half had pain. Half had  
17  swelling and erythema. About a third had warmth and  
18  about 15 percent had regional adenopathies. So for  
19  those of the panel that have taken care of these  
20  patients, they're often complicated and the diagnosis  
21  can be complex, I think as reflected by these clinical  
22  characteristics.

1                   Did you want me to answer the second  
2 question?

3                   DR. CARSON: I'm sorry. Go ahead, yes.

4                   DR. STEHMAN-BREEN: So with regard to the  
5 finding where in the third year the incidence of hip  
6 fracture, although they were very small numbers, was  
7 slightly greater in those subjects that were treated  
8 with denosumab, I think one thing that's important to  
9 note is that the fracture rate in the placebo group,  
10 hip fracture, was actually declining in that last  
11 year, whereas in the denosumab group it was staying  
12 the same. There was no time by treatment interaction.  
13 And it's possible, as you're alluding to, that this  
14 may reflect a survivorship phenomenon.

15                   You asked the question did subjects continue  
16 in the study after they'd had a hip fracture. They  
17 were, of course, invited to continue participation in  
18 the study. Many of them did continue in the study.  
19 There were some that at that point discontinued  
20 participation. But we did have subjects that were  
21 enrolled in the study were invited to continue the  
22 study even if they had been removed from

1     investigational product. And so we did make every  
2     effort to follow the subjects for as long as possible.

3             DR. CARSON: Dr. Rosen?

4             DR. ROSEN: Thank you. I have two lines of  
5     questions. The first relates to the discontinuation  
6     of denosumab in the two-year follow-up data. So can  
7     you give an estimate of the relationship between the  
8     change in BMD that occurs with denosumab over the  
9     first year after cessation of treatment, which is  
10    about 6 and a half percent, it comes down to zero, and  
11    its relationship to what happens with estrogen  
12    withdrawal?

13            Is it the same slope of change or is it more  
14    rapid? And if it is, how does that relate to the  
15    increase in fracture number that we saw in the  
16    individuals that were discontinued? There were nine  
17    in the denosumab and five in the placebo group in the  
18    132 study.

19            DR. STEHMAN-BREEN: Let me first start by  
20    answering the second part of your question and then we  
21    have some data available that shows changes in bone  
22    markers in relationship to estrogen therapy.

1           With regard to your second question about  
2 fracture rates, as you noted, there were more  
3 fractures in those subjects treated with denosumab  
4 during that off treatment period. However, when we  
5 looked at osteoporosis or osteoporotic fractures, the  
6 rates were similar with four nonvertebral osteoporotic  
7 fractures in the denosumab group and four in the  
8 treatment group.

9           Now, we have done a post hoc analysis  
10 subsequent to completion of the briefing document  
11 where we've looked at those subjects in the PMO  
12 fracture study that discontinued therapy over the  
13 course of the study but continued participating in the  
14 study. When we looked at those fracture rates, we  
15 included in this analysis subjects that had had at  
16 least seven months of follow-ups since their last dose  
17 of investigational product. And what you can see are  
18 the fracture rates per hundred years were similar  
19 between those treated with placebo and those treated  
20 with denosumab. Again, recognizing that it's not the  
21 perfect analysis, but it does give us some sense of  
22 fracture rates after discontinuation.

1           DR. ROSEN: But if I'm not mistaken, in the  
2    HALT breast cancer study, there was twice as much  
3    fractures, all fractures, after discontinuation of  
4    denosumab as well.

5           DR. STEHMAN-BREEN: Yes, you are correct  
6    that were more fractures in the discontinuation  
7    period. It's in the breast cancer study. It's  
8    important to keep in mind two things, one, these  
9    subjects, many of them continued on the aromatase  
10   inhibitors and had significant reductions in bone  
11   mineral density during that follow-up period. And  
12   when we looked carefully at the concomitant  
13   medications in those two populations, you can see in  
14   this figure that subjects in the placebo group were  
15   treated with alternative therapies, bisphosphonates  
16   typically, twice as frequently as those subjects  
17   treated with denosumab, making the analysis quite  
18   confounded.

19           In addition, in that study, all fractures  
20   were captured through adverse event reporting. And  
21   unlike our other study, with our study, the PMO  
22   prevention study, were not confirmed by a central

1 review.

2 DR. ROSEN: Just to follow up, though, the  
3 rate of change of 6.5 percent in the first year of  
4 loss, how does that relate to estrogen withdrawal and  
5 the turnover markers which go up considerably during  
6 the first year?

7 DR. STEHMAN-BREEN: Thank you. I'm going to  
8 have Dr. Javier San Martin, who was responsible for  
9 the conduct of this clinical trial, comment on that  
10 finding.

11 DR. SAN MARTIN: This is the study looking  
12 at discontinuation of HRT published a few years ago by  
13 Dr. Gallagher. And as you can see, the decrease in  
14 bone mineral density is similar to the one we see with  
15 denosumab discontinuation. In the upper panel, you  
16 see the lumbar spine bone mineral density and in the  
17 lower panel, you see the total hip. So both the  
18 increases in bone turnover and also the decrease in  
19 bone mineral density are relatively similar. And a  
20 similar finding was also seen with risendronate. So  
21 this --

22 DR. ROSEN: But Dr. Siris' part of the study

1     that looked at the post-estrogen follow-up in NORA and  
2     their rate of hip fractures were increased. So how do  
3     you balance that rapid change with the possibility  
4     that there could be an increased risk of fracture?

5             DR. SAN MARTIN: Yes, that was a finding in  
6     the NORA study. Also, for the numbers that were  
7     fractured, there was not an increased risk. And I  
8     think the more relevant study to look at this data is  
9     the WHI discontinuation. And in this study, which is  
10    a very large study that really in a more controlled  
11    fashion followed patients that discontinued hormone  
12    replacement therapy, there was no difference in hip  
13    fracture incidence.

14            DR. ROSEN: Right, except most of those  
15    women were not osteoporotic, correct?

16            DR. SAN MARTIN: That's true. The same  
17    applies for the NORA study.

18            DR. CARSON: Did you get your questions  
19    answered?

20            DR. ROSEN: Yes, thanks.

21            DR. CARSON: Dr. Bennett?

22            DR. BENNETT: I have three questions that



1 relate to skin infections. I'm more interested in the  
2 mechanism than I am concerned about the safety  
3 implications because these are easy to detect. There  
4 are complications of these. And particularly in the  
5 United States where so many of the elderly have  
6 replaced joints, you can have skin organisms, usually  
7 staphylococcal species infecting an existing  
8 prosthetic joint. Very few of the patients in this  
9 study were from the US, so I don't know how many  
10 prosthetic joints were in the elderly in this study.

11 But the other issue that will frame the last  
12 question, the third question that I have, is that the  
13 elderly are prone to skin infections at the lower  
14 extremities because of loss of skin elasticity as well  
15 as the frequent occurrence of dependent edema. So my  
16 three questions are first, with the endocarditis or  
17 joint infections due to skin organisms, in the handout  
18 the only one I found was an endocarditis turning staph  
19 aureus. I wondered if you knew about that. The  
20 other, I was surprised with the incidence of arthritis  
21 and I wondered how many of those were in prosthetic  
22 joints.

1           The last question is, is there a reason to  
2 think that the denosumab might have influence collagen  
3 deposition? Because if it did that, it might have a  
4 subtle or prolonged effect on skin elasticity, which  
5 could then explain increased incidence of infection in  
6 the lower extremities.

7           DR. EISENBERG: I think with regards to the  
8 third question, our preclinical data would not suggest  
9 there'd be an effect on collagen. The other two  
10 questions, we do have some information on. Again,  
11 Dr. Stehman-Breen looked at each of these, both the  
12 infective arthritis and the endocarditis, so I'll ask  
13 her to comment.

14           DR. STEHMAN-BREEN: So with regard to the  
15 infective arthritis cases, as you heard in the  
16 presentation, there were eight in the denosumab group  
17 in the fracture study, and there were none in the  
18 placebo group. But when we looked at these adverse  
19 events, none of them were serious adverse events.  
20 None of them required intravenous antibiotics, and  
21 none appeared to be a classic septic joint. And none  
22 of them had evidence of a joint replacement. And it

1 appeared, as we looked carefully at these cases and  
2 the way that these verbatim terms are reported, that  
3 if you report an infection at the knee, it maps to an  
4 infective arthritis. And therefore, it appeared that  
5 these were likely exacerbations of arthritis or in  
6 some cases cellulitis.

7 DR. BENNETT: That's clear. Thank you.

8 DR. EISENBERG: I'm happy to comment on the  
9 endocarditis. Some cardiologists offered to bring the  
10 slide up.

11 If we looked overall in our clinical  
12 experience and recognizing the citation to cases of  
13 endocarditis in the New England Journal, which looked  
14 at very careful case criteria, first of all, we did  
15 have additional cases in the placebo patients. So for  
16 the overall population, the difference is small. I  
17 reviewed all of these cases. Typically, one case  
18 clearly required a valve replacement, and so there  
19 clearly was documentation of endocarditis.

20 In the other cases, the cause of the  
21 pathogen was not defined, and it's a typical  
22 echocardiographic diagnosis of vegetations on the

1 valve. So we have one case clearly where we were  
2 certain that it's endocarditis.

3 My recollection of those cases was that  
4 these were incidental findings during these patients'  
5 hospitalizations so that a causative -- going back to  
6 the concern around skin, I don't believe we have any  
7 evidence that that would have been the case.

8 DR. BENNETT: Thank you.

9 DR. CARSON: Dr. Mortimer, back to you.

10 DR. MORTIMER: I'm sorry and I'm really not  
11 perseverating on this point, but the clarification  
12 about the breast cancer incidence. Because the fact  
13 is twice as many women went off study because of a  
14 diagnosis of breast cancer. Therefore, the drug was  
15 stopped. So ultimately, with stopping the drug, the  
16 incidence in breast cancers turned out to be  
17 equivalent. And I guess my concern in looking at that  
18 is does this drug somehow shorten the length time? Is  
19 there a length time bias? Does it sort of make these  
20 cancers more apparent earlier than they would have?

21 So is there a difference in how these  
22 cancers were diagnosed? I mean, were the treatment

1 more hypervigilant than the placebo group?

2 DR. EISENBERG: Sure, and that's a good  
3 question. And, of course, there is also the  
4 confounding in general that we had slightly more  
5 cancer deaths than in the placebo group that also  
6 censure some subjects. But perhaps Dr. Stehman-Breen  
7 can comment on the discontinuation.

8 DR. STEHMAN-BREEN: So there didn't appear  
9 to be any pattern that would suggest that these  
10 subjects were diagnosed earlier. You can see that we  
11 have timing of the breast cancer event, and you can  
12 see month 1 to year 1, year 1 to year 2, year 2 to  
13 year 3, they're relatively well balanced. It didn't  
14 appear that there was anymore rapid diagnosis of the  
15 disease certainly in the denosumab group.

16 There are many reasons that people  
17 discontinue therapy, and they can vary from living  
18 very far from an investigative site to having a  
19 support system that's needed for other reasons. And  
20 after a very thorough review, we've really been left  
21 with the conclusion that this doesn't appear to be due  
22 to phenotypic differences in the cancer and really is

1 a chance finding. But I'm happy to answer additional  
2 questions.

3 DR. EISENBERG: I think just to answer your  
4 question, Dr. Mortimer, to make sure we're clear on  
5 this because there isn't more censuring of cases.

6 So if you look at this slide, you can see  
7 that, in fact, you have a pretty balanced time for  
8 discontinuation. So the yellow shows the patients who  
9 discontinued relative to the last slide. And again,  
10 it's eight versus nine. It really seems to be  
11 independent of any of the other findings. So that's  
12 the specific answer.

13 DR. CARSON: Go ahead.

14 DR. MORTIMER: But the fact is the incidence  
15 went down when you discontinued the drug. It  
16 equilibrated to the placebo.

17 DR. EISENBERG: I don't believe that's true.

18 DR. STEHMAN-BREEN: They had already been  
19 diagnosed at the time that they discontinued so they  
20 would count --

21 DR. MORTIMER: Right, so my question  
22 continues to be are they found earlier because of this

1 drug somehow making them grow and becoming morp hic?

2 DR. STEHMAN-BREEN: There didn't appear to  
3 be any evidence of that. But let me ask Dr. Roger  
4 Dansey, who's our oncologist and who has been  
5 responsible for our oncology programs, to come to the  
6 microphone and perhaps we can provide an answer.

7 DR. DANSEY: So I think I can reiterate the  
8 points that have been made. The rates of new cancers  
9 are essentially the same on this study. The reasons  
10 for discontinuations are not apparent. The types of  
11 cancers, the clinical characteristics are similar.  
12 And I'm not sure that we necessarily connect the  
13 discontinuation rate because of the timing, as you  
14 saw, being scattered across those three years with  
15 necessarily some early effect of denosumab somehow  
16 bringing the cancer to the full -- in a quicker time  
17 period than on placebo arms.

18 DR. CARSON: Thank you.

19 Ms. Solonche?

20 MS. SOLONCHE: My first question is, can you  
21 provide any data on the percentage or numbers of  
22 clinical trial participants who suffered two or more

1 adverse events? While you think about that --

2 DR. EISENBERG: We could probably come back  
3 to you with that. I don't believe I have that readily  
4 available, but many subjects in terms of nonserious  
5 adverse events will report multiple adverse events.  
6 But I believe we can provide that to you perhaps after  
7 lunch. We'll see if we can give that information.

8 MS. SOLONCHE: Thank you.

9 The second question is, do you find that  
10 this monoclonal antibody has any effect on cancer  
11 antigen tests? For example, the CA-125 for ovarian  
12 cancer or any of the CEAs?

13 DR. EISENBERG: No, it's a very good  
14 question, but the antibody is very specific for human  
15 RANK ligand, so we wouldn't expect it to have any  
16 other binding activity.

17 MS. SOLONCHE: Okay. Thank you.

18 DR. CARSON: Dr. Richardson?

19 DR. RICHARDSON: Practices around the world  
20 certainly vary country to country and I think patients  
21 to patients, physicians to physicians. I was taken by  
22 one of the things that Dr. Stehman-Breen mentioned,



1   that most of the data on cataracts in I guess it was  
2   the prostate cancer trial were dependent on surgical  
3   reports. And it would seem to me that this must be a  
4   gross underestimate of the incidence of cataracts in  
5   this group.

6           DR. EISENBERG: This would have been new  
7   cataracts that were identified by the adverse event  
8   report of having the requirement for surgery. I think  
9   it's a fair point that without a properly conducted  
10   ophthalmologic study, I don't think we can say. If we  
11   bring up CTA, I think this sort of gives you a sense  
12   of how one would think about this in terms of  
13   background rights. And you're right. I mean clearly,  
14   a proper ophthalmologic examination identifies more  
15   subjects and it may be that you'd find something  
16   different than those who require surgery. So I think  
17   you're right about that, yes.

18           DR. RICHARDSON: Let me ask, make one other  
19   statement. Kind of woven throughout the applicant's  
20   materials and the FDA analyses, it seemed to me that  
21   there were instances in which there were important  
22   pieces of information that were lacking. Family

1 members not giving important pieces of information  
2 such as cause of death, which in these kinds of  
3 studies I think is extremely important, and it I think  
4 raises questions about the rigor with which some of  
5 this information was gathered. And I think these  
6 kinds of things really do, in fact, reflect on the  
7 integrity of the database as a whole.

8           We heard that only a small number of  
9 patients from US were entered. Can you tell us where  
10 these patients came from, where in the world and the  
11 kinds of practices that were recruited for this?

12           DR. EISENBERG: Absolutely. Dr. San Martin  
13 was involved in conducting the study, so I'll have him  
14 comment.

15           DR. SAN MARTIN: Thank you. Here we have  
16 the distribution of patients in the Study 216, which  
17 is the PMO study. As you can see, about 45 percent of  
18 patients came from Western Europe, 34 from Eastern  
19 Europe, 12 from Latin America, 7.4 North America, and  
20 1.2 percent from Australia and New Zealand.

21           DR. CARSON: Question's answered,  
22 Dr. Richardson? Okay.

1 Dr. Collins?

2 DR. COLLINS: Yes, hi. I had questions  
3 about the hypocalcemia and the related mineral  
4 metabolism, the physiology related to that.

5 So given the very dramatic degree of  
6 suppression of bone turnover, I'm actually surprised  
7 that there wasn't more hypocalcemia and wondered about  
8 then what compensated for that. And it must be  
9 secondary hyperparathyroidism or elevations in  
10 parathyroid hormone and subsequent elevations in  
11 125-D.

12 So one question would be then, do you have  
13 the data on the degree of secondary  
14 hyperparathyroidism and how prolonged that is, the  
15 data on 125-D levels? And related to that then, were  
16 cases of hypocalcemia more common in patients that  
17 were 125-D deficient? Were they more common in  
18 patients with renal insufficiency who couldn't mount a  
19 125-D response?

20 DR. EISENBERG: We have some of the answers  
21 to that. Again, remember, of course, in the pivotal  
22 trials, everybody was supplemented as well with

1 calcium and Vitamin D, which certainly helps. But I  
2 think Dr. Stehman-Breen can answer some of the  
3 questions that you're getting at. We can't answer  
4 them all.

5 DR. STEHMAN-BREEN: With regard to your  
6 question about the compensatory mechanisms, you're  
7 correct. This slide illustrates the transient  
8 increases that are observed in PTH that are observed  
9 consistently across studies. And on the right side of  
10 the panel, you can see the reductions in serum  
11 calcium. And so they are well coupled with each other  
12 but are transient.

13 I think your second question was whether or  
14 not these levels of -- oh, you asked about Vitamin D.  
15 So we measured Vitamin D at baseline. We didn't do  
16 additional assessments of Vitamin D throughout the  
17 study. As Dr. Eisenberg pointed out, everybody was  
18 supplemented throughout the study. We did do  
19 assessments looking at whether reductions in calcium  
20 varied by whether or not someone's Vitamin D level was  
21 greater or less than 20, between 12 and 20, and there  
22 didn't appear to be a significant difference.

1           We looked carefully with regard to renal  
2   function. And generally, there was slightly greater  
3   reduction in serum calcium in those subjects. This is  
4   in our PMO fracture study. And those subjects with  
5   greater degrees of renal dysfunction but levels of  
6   calcium less than 7.5 were unusual. And as you can  
7   see, were also observed in the placebo group. So with  
8   regard to renal function, with supplementation of  
9   calcium and Vitamin D, it appears to compensate for  
10   inability to convert to active Vitamin D at very low  
11   levels of renal function.

12           DR. CARSON: Did you get your question  
13   answered?

14           DR. COLLINS: Yes, I did. And I guess so  
15   there clearly was development of secondary  
16   hyperparathyroidism, but it appeared to be relatively  
17   transient.

18           But I wondered, there seems to be some  
19   evidence of secondary hyperparathyroidism on some of  
20   the bone biopsy specimens, particularly the case of  
21   marrow fibrosis, the trabecularization of the bone  
22   marrow. And I wonder if this could be the effect of

1 chronic secondary hyperparathyroidism.

2 DR. STEHMAN-BREEN: So just to clarify, the  
3 marrow fibrosis was in a subject treated with  
4 alendronate. I'd like to ask Dr. --

5 DR. COLLINS: Alendronate alone or  
6 alendronate --

7 DR. STEHMAN-BREEN: Just alendronate.

8 I'd like perhaps to have Dr. Dempster come  
9 to the microphone and comment on your second question  
10 with regard to PTH and bone biopsies.

11 DR. DEMPSTER: Thank you very much. My name  
12 is David Dempster. I'm a professor of clinical  
13 pathology at Columbia University in New York. I  
14 wanted to specifically comment on the one biopsy and  
15 Dr. Collins' question.

16 The biopsy was taken long after -- this was  
17 a 36-month biopsy, so that would be long after any  
18 transient increase in PTH.

19 This is a void in the cortex that we see  
20 quite routinely in patients with osteoporosis. As  
21 seen here, it is described in the FDA document as  
22 resorption. However, if we go to a higher power

1 slide, you can see that the inner aspect of the void  
2 is lined by osteoid and osteoblasts. So this is a  
3 formation site at this point and clearly is filling  
4 in.

5           The sponsor went back and looked at micro CT  
6 images because of the concern raised. You can see  
7 this is a paired biopsy. One was taken at month 24,  
8 and one was taken at month 36. And it's month 36  
9 where this anatomical variant was observed. Clearly,  
10 the month 36 biopsy is taken from a different  
11 anatomical site. You can see that it's substantially  
12 bigger.

13           Interestingly, while the void can be seen in  
14 one orientation, if it is rotated through 90 degrees,  
15 as you can see, the void disappears. So I think this  
16 tells us that this is a very localized porosity within  
17 the cortex. And furthermore, if you look at the lower  
18 image, again the right-hand image, which is a  
19 reconstructed micro CT image of this specimen, you can  
20 see that there is good connectivity between cancellous  
21 bone and cortical bone. So I think the implication  
22 that this would result in a significant loss of bone

1 strength is not true in this particular case.

2 DR. CARSON: Let me just say there are about  
3 four more questions in the queue and we'll go ahead  
4 and get as many of these answered until 12:15 and then  
5 break for lunch. And then those that are left over,  
6 we do have time for more questions this afternoon.

7 I do have a question. And that is, I  
8 noticed in the material that you've presented to us  
9 that the benefit of the drug with bone mineral density  
10 in Study 216 decreased compared to placebo as body  
11 weight increased. And because such a large percentage  
12 of the participants were not from the United States,  
13 and perhaps in countries where weight is not as much  
14 of a health problem, I wonder if you have more  
15 information on the weight of these subjects and how it  
16 affected outcome.

17 DR. EISENBERG: My understanding is -- and  
18 I'll ask Dr. San Martin to comment -- that there  
19 wasn't a relationship between body weight and  
20 efficacy. But perhaps Dr. San Martin can comment.

21 DR. SAN MARTIN: Thank you. This is a  
22 typical finding, which is that increase in bone



1 mineral density, bone mineral density on the baseline  
2 weight. So it is commonly observed that patients who  
3 have higher body mass in this -- or heaviest, they  
4 have baseline higher bone mineral density. And  
5 because their bone mineral density is present as  
6 percent change, you usually see less increase in terms  
7 of percent change in those patients who have higher  
8 BMI, or body mass index, or heaviest weight.

9 I don't know if we have a slide that  
10 specifically look at this, but a bar figure, a  
11 different baseline body weight.

12 DR. EISENBERG: Can you comment? I think  
13 Dr. Carson also was interested in the body weight  
14 distribution in the 216 trial?

15 DR. SAN MARTIN: Right. So the mean BMI was  
16 about 25, which is typically seen in osteoporosis  
17 patients. I don't really have data to compare that  
18 with the US population in general. I don't know if  
19 that answered your question.

20 DR. CARSON: I'm sorry. I remembered  
21 incorrectly. You state that the effects of the drug  
22 in preventing new vertebral fractures were rapid and

1     sustained statistically significant differences  
2     between the drug and placebo groups were observed.  
3     But the differences decreased with increasing body  
4     weight.

5             DR. SAN MARTIN:   So I referred to bone  
6     mineral density, but we do have the data looking at  
7     vertebral fracture by weight.

8             Here you see the primary efficacy data as  
9     has been presented before which shows a 68 percent  
10    reduction in new vertebral fracture.  And when you  
11    look at the different baseline body weight, you see  
12    that the risk reduction is very consistent, going from  
13    72 percent to 65 percent in those patients with higher  
14    BMI or higher baseline weight.

15            DR. CARSON:  Thank you.

16            Dr. Rosen?

17            DR. ROSEN:  I'd like to explore the  
18    suppression in bone turnover and get a sense from the  
19    sponsor about their feeling about the absence of label  
20    in 36 percent of the month 36, and then explore with  
21    you a little further the relationship of the absence  
22    of detectable CTX to the absence of labels.

1           So could you start with a little discussion  
2 about your interpretation of the absence of any label?

3           DR. STEHMAN-BREEN: So as you're alluding  
4 to, there was absence of label in either the cortical  
5 or trabecular bone in approximately one-third of the  
6 subjects in which we conducted bone biopsies. This  
7 is consistent with the mechanism of action of  
8 denosumab and the level of suppression of bone  
9 turnover that we've seen with the serum marker CTX.

10           The clinical implications of that reduction  
11 in the amount of labeling in bone, we can comment on  
12 with regard to the three years of follow-up in our  
13 pivotal fracture study and those data you've heard.  
14 We've also not demonstrated any adverse impact of that  
15 level of bone turnover reduction as reflected by  
16 labeling in terms of atypical fractures or  
17 abnormalities in fracture healing, or abnormalities in  
18 healing of fractures.

19           We are committed to continuing to monitor  
20 this in our long-term safety program, as we recognize  
21 that the safety of the drug, the long-term safety, can  
22 only be defined by those sorts of programs. In

1 addition, we have bone biopsies that will be conducted  
2 as part of that long-term extension study to help us  
3 continue to understand what the bone histology and  
4 histomorphometry appears over long-term with long-term  
5 treatment of denosumab.

6 DR. ROSEN: Have you looked at the  
7 demographic characteristics of those individuals that  
8 have these suppressed -- the absence of the label and  
9 how that might relate either to the absence of  
10 detectable CTX in your subjects?

11 I mean, I think the issue here is, can we  
12 pick out those individuals that could be at particular  
13 risk for suppression, for marked suppression, in  
14 turnover, which then subsequently might put them at  
15 risk for atypical fractures down the road?

16 DR. STEHMAN-BREEN: There haven't been any  
17 variables that have been able to predict those  
18 subjects that are going to have a lack of label. And  
19 it's also again consistent with our mechanism of  
20 action. So although if we could potentially identify  
21 a risk factor for lack of label, it ultimately would  
22 be most relevant if we did find that there was an

1 adverse outcome associated with that level of  
2 suppression.

3           It's important to keep in mind that  
4 denosumab is reversible. And so unlike  
5 bisphosphonates, if we did see an adverse outcome,  
6 associated this with long-term treatment of denosumab,  
7 we do have the ability to discontinue the therapy with  
8 return of osteoclast function.

9           DR. ROSEN: So I understand that that's the  
10 mechanism of action, but we're not used to seeing the  
11 absence of label in a third of the subjects. And so I  
12 think we need some clarification about what the  
13 importance of that is. We're not making any  
14 judgments; we're just trying to understand or  
15 appreciate how that compares to bisphosphonates such  
16 as zoledronic acid where label was present in 81 out  
17 of 82 subjects. So can you give us some clarification  
18 on that?

19           DR. STEHMAN-BREEN: Yes, I understand your  
20 concern, and I think what I'll do is perhaps have  
21 Dr. Dempster come to the microphone and address your  
22 question.

1           DR. DEMPSTER: Thank you. As the panel is  
2 well aware, remodeling serves two main functions. One  
3 is metabolic, as Dr. Kehoe has mentioned, and the  
4 iliac crest and cancellous bone, specifically in the  
5 iliac crest, is considered to be a highly  
6 metabolically active site. The other function is  
7 mechanical repair. And at that particular site in the  
8 iliac crest, there is very little need for mechanical  
9 repair because it's not a weight-bearing site nor is  
10 it a fracture site. And, in fact, if you look for  
11 micro damage at the iliac crest, there are vanishingly  
12 small amounts of micro damage.

13           So the trigger for targeted remodeling and  
14 mechanically necessary remodeling is very low at that  
15 site. I therefore think it's reasonable to assume  
16 that we could see almost complete or indeed complete  
17 suppression of remodeling at that site without losing  
18 the necessary remodeling that is mechanically driven  
19 at other sites.

20           To support that, if I could have slide 49,  
21 this is an analysis similar to the one that Dr. Kehoe  
22 presented. But what I asked the sponsor to do was

1 look at the patients who had no label, and they're  
2 shown with the yellow label third from the left at  
3 both month 24 and month 36, and compare that, looking  
4 at serum CTX values, with patients who either had  
5 single or double label to the left of these lines or  
6 to the placebo group, to the right of the line with no  
7 label. And what you see is there's substantial  
8 overlap.

9           Clearly, this is later on in the treatment  
10 course. These CTX values were not taken at month 1.  
11 They were taken at the time of the biopsy. But I  
12 think what this tells us is that even if there's no  
13 label in the biopsy, in a substantial number of these  
14 people, there is still remodeling occurring at a  
15 substantial rate at other parts of the skeleton.

16           DR. CARSON: Go ahead, Dr. Rosen.

17           DR. ROSEN: I just want to follow up with  
18 one final informational question, and I'm not sure if  
19 Dr. Dempster can answer that. But the strength  
20 testing that you did, I understand the absence of  
21 rodent model, but relative to this, the strength  
22 testing you did was vertebral strength testing, did

1    you do repetitive cyclic testing to look for fatigue  
2    or was this purely vertebral testing?

3               DR. EISENBERG:   Let me ask Paul Kostenuik  
4    who is responsible for the preclinical program in  
5    terms of bone studies.

6               DR. KOSTENUIK:   Thank you for the question.  
7    We only performed monotonic testing, destructive  
8    compressive testing of the vertebrae and other sites.

9               DR. ROSEN:    Sorry, Paul.   Was that just the  
10   vertebrae?

11              DR. KOSTENUIK:   We assessed whole vertebral  
12   bodies, and we also assessed trabecular cores from the  
13   vertebrae.   And all of those analyses in three  
14   separate studies showed improvements in the structural  
15   properties of bone strength and no reductions in any  
16   of the material properties we measured.

17              DR. CARSON:    Dr. Emerson, final question  
18   before lunch.

19              DR. EMERSON:    This is a question about the  
20   diverticulitis that you did, and maybe I'm just  
21   parading how bad a student I was in medical school.  
22   But I thought diverticulitis was the infection and the



1   diverticulum was just an anatomic risk factor for  
2   having diverticulitis. So why would we be interested  
3   in including the diverticulum in there if, in fact,  
4   what this treatment might have done is increased the  
5   risk of diverticulitis among those with diverticula?

6           DR. EISENBERG: Sure, I'll have  
7   Dr. Stehman-Breen comment briefly about the aggregated  
8   cases. But part of this is, as we've highlighted,  
9   MEDRA is quite useful in terms of providing a means to  
10   code cases. You have to look at the individual  
11   clinical cases. I would say when you do that for  
12   diverticulitis, there's still some small differences.  
13   But we can provide some additional context.

14           DR. STEHMAN-BREEN: So you are correct in  
15   your recollection from medical school. But when we  
16   went back and looked carefully, as Dr. Eisenberg  
17   noted, there are some challenges in just looking at  
18   the preferred terms. And for the serious adverse  
19   events, we had very detailed case reports. We were  
20   able to look at all of the adverse events, including  
21   diverticulum serious adverse events that may be  
22   related to diverticulitis or may be diverticulitis.

1 And, in fact, we did have a total of two cases in the  
2 placebo group and two cases in the denosumab group  
3 that weren't coded as diverticulum. But when you read  
4 the cases, they actually indicated they were  
5 diverticulitis.

6 DR. CARSON: Dr. Emerson is clearly hungry,  
7 and Dr. Goozmer had a question. If we can save that,  
8 we'll start our afternoon session with that.

9 We'll break for lunch now. It will be  
10 served in the restaurant you can reach by going out  
11 the hall, turning left, and going through the lobby.  
12 And then we'll reconvene at 1:00 and start the open  
13 public session shortly thereafter.

14 Please take any personal belongings with you  
15 at this time. And committee members, please remember  
16 that there should be no discussion about the meeting  
17 during lunch with each other, with the press, or with  
18 any member of the audience. Thank you.

19 (Whereupon, at 12:160 p.m., a lunch recess  
20 was taken.)

21

22

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

2                   DR. CARSON: Welcome back. We'll begin the  
3 afternoon session with the public hearing.

4                   Both the Food & Drug Administration and the  
5 public believe in a transparent process for  
6 information gathering and decision-making. To ensure  
7 such transparency, at the open public hearing session  
8 of the Advisory Committee meeting, FDA believes that  
9 it is important to understand the context of an  
10 individual's presentation.

11                  For this reason, FDA encourages you, the  
12 open public hearing speaker, at the beginning of your  
13 written or oral statement to advise the committee of  
14 any financial relationship that you may have with the  
15 sponsor, its product, and if known, its direct  
16 competitors. For example, this financial information  
17 may include the sponsor's payment of your travel,  
18 lodging or other expenses in connection with your  
19 attendance at the meeting.

20                  Likewise, FDA encourages you at the  
21 beginning of your statement to advise the committee if  
22 you do not have any financial relationships. If you

1 choose not to address this issue of financial  
2 relationships at the beginning of your statement, it  
3 will not preclude you from speaking. The FDA and this  
4 committee place great importance in the open public  
5 hearing process. The insights and comments provided  
6 can help the agency and this committee in their  
7 consideration of the issues before them.

8           That said, in many instances and for many  
9 topics, there will be a variety of opinions. One of  
10 our goals today is for this open public hearing to be  
11 conducted in a fair and open way where every  
12 participant is listened to carefully and treated with  
13 dignity, courtesy and respect. Therefore, please  
14 speak only when recognized by the chair and thank you  
15 for your cooperation.

16           The first speaker is Kathleen Cody, the  
17 Executive Director of the Foundation for Osteoporosis  
18 Research and Education and the American Bone Health.

19           MS. CODY: Thank you. I have no disclosures  
20 about my travel to be here at this meeting today, but  
21 as a non-profit organization, I do receive financial  
22 support from most of the pharmaceutical companies and

1 other industry individuals and companies.

2 I'm here to represent the 44 million  
3 Americans who are affected by osteoporosis and low  
4 bone mass. Only a few of them know that I'm here  
5 today, and in fact, only a few of them -- most of them  
6 don't even know that they are at risk for  
7 osteoporosis.

8 So how can that be? This disease is going  
9 to touch the lives of so many people. In fact, many  
10 of the people in this room are going to be touched by  
11 osteoporosis in their lifetime. It might not be you,  
12 but it will be perhaps your grandmother or your mother  
13 or your sister or your father or perhaps even a  
14 friend.

15 Osteoporosis is terribly overlooked by both  
16 patients and by doctors. So how can that be? Is it  
17 the age of the patients that are affected by  
18 osteoporosis? Is it the fact that they're mostly  
19 women who are affected by osteoporosis? Or is it that  
20 people think it's normal to shrink several inches as  
21 they get older.

22 So how would you ever know if you had

1 osteoporosis since it's a silent disease? Well, you  
2 could be tested. A bone density test is more accurate  
3 in predicting fractures than blood pressure is of a  
4 stroke, or cholesterol is of a heart attack. A bone  
5 density test is pretty simple. It's not painful and  
6 right now, it doesn't cost very much. And yet only 13  
7 percent of the women of Medicare age in 2008 were  
8 tested for osteoporosis.

9           So if you had a bone density test and found  
10 out that you were at moderate or high risk for having  
11 a fracture, wouldn't that give you some motivation to  
12 make some changes in your lifestyle and maybe get  
13 treated to avoid a fracture? So if people aren't  
14 tested, they find out they have osteoporosis when a  
15 bone breaks. Osteoporosis is the leading cause of  
16 fractures among older adults and it always results in  
17 bad outcomes: immobility, disability, and even death.

18           With this knowledge, wouldn't it surprise  
19 you that 78 percent of the individuals who have  
20 fractures are never evaluated for the underlying  
21 cause, which in many cases is osteoporosis and then  
22 treated to prevent more fractures?

1           We have lots of fractures that could be  
2 prevented. There were two million in 2005. In fact,  
3 today while we're at this Advisory Committee meeting,  
4 there will probably be about 1,500 fractures related  
5 to osteoporosis.

6           So if disability, pain, and even death don't  
7 worry you enough, perhaps knowing that fractures cost  
8 this country over \$21 billion. That's \$21 billion in  
9 2007. And left unfettered and compounded by our aging  
10 population, the costs are expected to skyrocket to  
11 \$25 billion by the year 2025.

12           So these are pretty dismal statistics that  
13 I'm sharing with you today and we're here together, I  
14 hope, to start to change them. We need as many tools  
15 and as many partners in this fight as we can get.  
16 There's a role for everyone and everyone has a role in  
17 making a difference here. So as a committee, you're  
18 here to determine whether this is an appropriate drug  
19 to use in this fight against osteoporosis.

20           I would like to thank you on behalf of all  
21 of the people who are risk for osteoporosis or have  
22 osteoporosis. I would like to thank Amgen for their

1 work over all these years in bringing us yet another  
2 tool as a possible solution to the treatment of  
3 osteoporosis. And I'd also like to thank the private  
4 donors of my organization who made it possible for me  
5 to be here today.

6           So Madam Chairman, if it's acceptable to  
7 you, I have a document that more deeply outlines the  
8 history of what's been done to date in the fight  
9 against osteoporosis, and also a book of photographs  
10 and stories of patients who've been affected by this  
11 disease I'd like to leave for the record.

12           DR. CARSON: Thank you. If you would just  
13 leave it for now with our transcriber.

14           Next is Roberta Biegel of the National  
15 Osteoporosis Foundation.

16           MS. BIEGEL: Good afternoon. I've received  
17 no financial assistance to be here today and I'm  
18 speaking on behalf of the National Osteoporosis  
19 Foundation, which accepts financial support from  
20 individual donors, foundations and corporations,  
21 including pharmaceutical companies in the form of  
22 educational grants.



1           The National Osteoporosis Foundation is  
2   appreciative of the opportunity to address the  
3   committee on the prevalence and burden of osteoporosis  
4   and the need for effective therapies for millions of  
5   Americans with and at risk for osteoporosis.

6           NOF is the nation's leading voluntary health  
7   organization solely dedicated to osteoporosis and bone  
8   health. It's mission is to prevent osteoporosis and  
9   related fractures, to promote lifelong bone health, to  
10   improve the lives of those affected by the disease and  
11   to find a cure thorough programs of awareness,  
12   advocacy, research and education. NOF is pleased to  
13   be a resource for the Food and Drug Administration.

14           As you've heard today, osteoporosis is a  
15   disease characterized by low bone mass, deterioration  
16   of bone tissue and architecture, compromised bone  
17   strength and an increase in the risk of fracture,  
18   especially the hips, spine and wrist, although any  
19   bone consequently can be affected. In simpler terms,  
20   osteoporosis weakens bones so that they break easily.

21           Osteoporosis is an intermediate outcome for  
22   fractures and is a risk factor for fracture, just as

1 hypertension is for stroke or high cholesterol is for  
2 heart attack. Fractures due to osteoporosis are  
3 common, costly, and often become a chronic burden on  
4 individuals and society.

5           Osteoporosis is often called a silent  
6 disease because bone loss often occurs without  
7 symptoms. People may not know that they have  
8 osteoporosis until their bones becomes so weak that a  
9 sudden strain, a bump or a sneeze, causes a fracture  
10 or a vertebrae to collapse. Collapsed vertebrae  
11 initially may be felt or seen in the form of severe  
12 back pain, loss of height, or spinal deformities such  
13 as a stooped posture.

14           Individuals with very severe osteoporosis  
15 may have difficulty breathing or even digesting their  
16 food, because their respiratory or digestive systems  
17 are so compressed that they are unable to function  
18 adequately. Osteoporosis may keep people from getting  
19 around easily and doing the tasks and activities that  
20 they enjoy and need to do on a daily basis.

21           This can cause people to feel isolated and  
22 depressed and sometimes can lead to other health

1 problems such as people being afraid to leave their  
2 home for fear of falling or they may not be able to  
3 shop for groceries and have adequate food and a  
4 balanced diet, or they may lack physical activity and  
5 they may not be able to meet with friends and  
6 socialize. These individuals often are invisible in  
7 our society and they often don't receive the medical  
8 care and support that they need.

9           There are multiple risk factors that  
10 increase the likelihood of developing osteoporosis and  
11 fractures. And as you've heard today, certain  
12 medicines and treatments for cancer might be a cause  
13 for osteoporosis.

14           NOF estimates that 44 million Americans have  
15 osteoporosis or are at risk for developing the disease  
16 because of low bone mass. That represents 55 percent  
17 of the population 50 years and older. And by 2020,  
18 the number of those with or at risk for the disease  
19 will increase to 61 million. A recent study estimates  
20 that by 2025, there will be three million fractures.  
21 Osteoporotic fractures also account for more than  
22 4 million hospital admissions, about 2.5 million

1 physician visits and more than 180,000 nursing home  
2 admissions. A woman's risk of hip fracture is equal  
3 to her combined risk of breast, uterine and ovarian  
4 cancer.

5           NOF in concert with its partners at the  
6 National Coalition for Osteoporosis and Bone Diseases  
7 in 2008, convened a meeting of 150 stakeholders to  
8 develop a national action plan and agenda to advance  
9 bone health promotion and disease prevention. Meeting  
10 participants built on the findings and recommendations  
11 of the 2004 Surgeon General's Report on bone health  
12 and osteoporosis.

13           The discussions were the basis for a  
14 national action plan for bone health, recommending  
15 steps for advancing bone health across the United  
16 States and one of the priority areas is to improve  
17 diagnosis and treatment. NOF is pleased that as a  
18 result of the research performed during the last 15  
19 years, patients and their physicians now have a choice  
20 of osteoporosis medications that can prevent and  
21 reduce the risk of the disease.

22           However, because of individual differences

1    there remains a continuing need for new, safe and  
2    effective osteoporosis medications.  Although  
3    osteoporosis is most commonly diagnosed later in life,  
4    it's not an inevitable consequence of aging.  It's a  
5    disease that's largely preventable and treatable.  
6    Individual differences should be considered by  
7    healthcare professionals to determine what they can do  
8    to prevent or treat osteoporosis.

9               A bedridden person in a nursing home who  
10   takes multiple medicines clearly can be viewed  
11   differently from the person who is physically active  
12   and does not suffer from other ailments.  Although  
13   many individuals remain undiagnosed and untreated, and  
14   you just heard fewer than 15 percent of women,  
15   Medicare beneficiaries, eligible for osteoporosis  
16   testing, take advantage of this benefit.

17              Those who are diagnosed and treated, often  
18   do not adhere to treatment.  Unlike with some other  
19   diseases, a patient initially and for a long time may  
20   have no indication that their medication is working  
21   and that their bones are getting stronger.  Their  
22   improved bone mass and reduced fracture risks are not

1 readily apparent and need time to develop. Usually  
2 they will not have a bone density test for two years.  
3 Sometimes after one year, if the physician thinks it's  
4 appropriate. Without obvious feedback, many patients  
5 lose motivation to continue with their osteoporosis  
6 medication.

7           The burden of medication for older people  
8 and post-menopausal women specifically can be very  
9 substantial. People agree that sub-optimal compliance  
10 with osteoporosis medications persistently decreases  
11 over time. Unfortunately, the long-term consequences  
12 of not complying is decreased bone density and  
13 sometimes worse.

14           In conclusion, the incidence of osteoporosis  
15 is estimated to increase and according to the surgeon  
16 general, the consequences of poor bone loss are  
17 disability, diminished function and loss of  
18 independence or premature death. Because of the  
19 complexity of osteoporosis and lack of adherence to  
20 treatments, NOF believes there's a critical need for a  
21 broad array of medications to prevent and treat the  
22 disease. With a wide range of approved, safe and

1 effective medications for the prevention and treatment  
2 of osteoporosis, physicians and patients may agree on  
3 an individualized approach to improving a patient's  
4 bone health. Thank you.

5 DR. CARSON: Thank you.

6 Marilyn Brown?

7 MS. BROWN: I live in Silver Spring,  
8 Maryland; travel to Bethesda, Maryland for my  
9 treatment and they pay for my parking. I was  
10 diagnosed with osteoporosis in my mid-sixties. I was  
11 put on Fosamax which permanently damaged my esophagus  
12 causing daily heartburn and I still take medicine  
13 daily for that. I was referred to Dr. Michael  
14 Bolognese. My current study is denosumab and this is  
15 my second study.

16 My bone density has increased 15 percent in  
17 the last three years. I am 83 years old and a very  
18 active person. I play tennis two to four times a  
19 week, clean my own home, cultivate, plant and harvest  
20 the vegetable garden, pick our strawberries,  
21 raspberries and blueberry plants, prune 21 shrubs, a  
22 hedge, two plum trees and a peach tree.

1           I'm a retired microbiologist who worked in  
2   clinical micro at NIH, National Institutes of Health,  
3   for 21 years. And after donating blood to Chemistry  
4   Clinical Department for research, I really believe  
5   strongly in research.

6           At 51 years of age, I slipped on black ice  
7   on my driveway, breaking a leg in three places  
8   resulting in a full cast for five months. At 73, I  
9   had eye surgery for a detached retina resulting in no  
10   tennis, et cetera, for six months and severely limited  
11   activities. My current research program is  
12   administered very professionally and thoroughly by  
13   Carol Bolognese, to whom I am very grateful. Thank  
14   you.

15           DR. CARSON: Thank you.

16           Gladys Quinterro?

17           MS. QUINTERRO: Good afternoon. My name is  
18   Gladys Quinterro and I am a Hispanic American woman.  
19   I am single, retired, and live alone in Arlington,  
20   Virginia and I am a very active senior citizen. I  
21   volunteer most of my day for an Arlington senior  
22   center where I assist with activities including the



1 daily luncheons.

2           Everyday I see the effect of poor health and  
3 the consequences of becoming frail. People are afraid  
4 to come when it rains or they stop coming all together  
5 because they are afraid of falling and have fallen and  
6 have a fracture.

7           I also volunteer and participate in many  
8 cultural activities. I am very active. In general, I  
9 walk to the senior citizen center -- an hour and  
10 twenty minutes a day. I mostly use public  
11 transportation. I love to travel in the United States  
12 and abroad. Often, we might backpack.

13           In general, I am blessed with good health  
14 and I have a wonderful quality of life. Five years  
15 ago, I was told I have significant osteoporosis. I  
16 volunteered for research study in which I received a  
17 shot every six months -- a shot every six months  
18 along with calcium and Vitamin D. I have a had quite  
19 a few falls, quite often, quite brutal, and have no  
20 broken bones. I went to classes to help me learn how  
21 to prevent falling. Also the medicine has helped me a  
22 great deal.

1           I am receiving most help -- all this  
2   medicine has protected me very well in my health. I  
3   am grateful for the five years I am able to do all  
4   activities and enjoy it.

5           In the program, I agreed to have a bone  
6   biopsy and hope that it will be shown that the  
7   medicine was safe and effective and for me and for  
8   anyone who will need to take it. Next week I will  
9   have another bone biopsy after five years of studies.

10          I thank you all on behalf of the women who  
11   have taken these injections to hopefully give women  
12   with osteoporosis an easy way to receive treatment and  
13   stay enjoying their quality of life. I have not  
14   received any financial support for these from anybody.  
15   I am a volunteer. I thank you.

16          DR. CARSON: Thank you.

17          Next is Laurel Glassman.

18          MS. GLASSMAN: Good afternoon. I am counsel  
19   to the law firm of White & Case, resident in the  
20   Washington, D.C. office. I have no affiliation or  
21   financial relationship to disclose. I am also a 60-  
22   year-old woman with osteoporosis. I was diagnosed

1 with osteopenia on my 50th birthday at menopause.

2 This rapidly progressed to osteoporosis in two years.

3 Both of my grandmothers had osteoporosis.

4 One died of the disease after breaking her hip. My

5 mother died of breast cancer at 56, but by that age

6 already was developing a dowager's hump. None of the

7 medications I have taken for my osteoporosis over the

8 past nine years appears to have worked for me and I am

9 not a candidate for hormone replacement therapy.

10 These medications include Fosamax, Evista,

11 Miacalcin, Actonel and Forteo. I was one of the

12 4 percent of patients on Forteo who did not show any

13 increase in bone density after two years on the

14 regimen. I'm currently still taking Actonel and

15 Evista and watching my bone density continue to

16 decline. For me and other people like me who have not

17 had a positive response to currently available drugs

18 for osteoporosis and over-the-counter Vitamin D,

19 calcium plus weight bearing exercise, efforts to find

20 and improve new drugs to effectively treat this

21 disease are urgently needed.

22 I worry everyday about what osteoporosis

1 will mean for my long-term future and hope that the  
2 FDA will continue to approve medications such as  
3 denosumab, if proven to be safe and effective  
4 treatments for osteoporosis. Thank you.

5 DR. CARSON: Thank you.

6 The next presentation will be by Seth  
7 Ginsberg, president of the Global Healthy Living  
8 Foundation.

9 MR. GINSBERG: I have no disclosures to make  
10 today regarding my travel here. The Global Healthy  
11 Living Foundation and CreakyJoints does accept grants  
12 and donations from many pharmaceutical companies as  
13 well as government and private foundations.

14 Good afternoon. On behalf of the Global  
15 Healthy Living Foundation, a 501(c)(3) patient  
16 advocacy group, and specifically on behalf of  
17 CreakyJoints, the 32,000 member bone and joint disease  
18 community that is a part of a the Global Healthy  
19 Living Foundation, I'd like to thank the committee for  
20 allowing me to speak about osteoporosis, a globally  
21 recognized priority health issue with economic and  
22 quality of life costs equal to and sometimes greater

1    than many much better known diseases.

2                   My name is Seth Ginsberg, a co-founder of  
3    CreakyJoints and the Global Healthy Living Foundation.  
4    I was diagnosed with spondyloarthritis at 13. By 15, I  
5    was a national spokesperson for the Arthritis  
6    Foundation. And at 18, when I went away to college,  
7    200 miles from home, I quickly realized the need for a  
8    positive supporting community to share strength and  
9    experience with experts and other patients alike.  
10   CreakyJoints was the result of this need. Today, 10  
11   years later, we have a vibrant community that  
12   participates in online as well as local community  
13   events held throughout the country.

14                  It is in this outreach context that I am  
15   speaking here today, representing our members with  
16   bone loss whether it occurs from ablation therapy or  
17   post-menopausal osteoporosis. Our members are  
18   information seekers. They tend to have higher than  
19   normal compliance and seek individual initiatives in  
20   order to continually improve their quality of life.

21                  Our members want to know what treatment  
22   options are available to them, how safe they are, how

1 much they cost, and how easy they are to take. We  
2 take their voices to the media, government,  
3 pharmaceutical companies, employers, third party  
4 payers, and the general public in an effort to  
5 educate, inform, and persuade these audiences to pay  
6 special attention to our community. This is why I am  
7 here today, to provide all the persuasion I can in  
8 support of denosumab and other new drugs that will  
9 expand the treatment options for doctors, patients,  
10 and caregivers to consider. Although I was not here  
11 earlier today, I am sure previous speakers have spoken  
12 much more authoritatively about the seriousness of  
13 this disease and the pressing need for pharmacological  
14 options, and in the case of ablation therapy, the  
15 first option.

16           The cost issue alone speaks to the critical  
17 need for a wide variety of treatment options. Early  
18 diagnosis and aggressive treatment are necessary in  
19 order to reduce the costs associated with fractures.  
20 These are unnecessary costs when treatments can  
21 improve bone mineral density.

22           Treatment can prevent fractures and the

1 economic cost and emotional trauma associated with  
2 osteoporosis. We've seen this firsthand. Ongoing  
3 education, a supportive environment, and individual  
4 initiatives, such as incorporating diet and exercise  
5 into a personal identity, are goals we try to reach at  
6 CreakyJoints.

7           We think government and industry can support  
8 us in this effort by continuing to monitor the  
9 effectiveness and safety of drugs our members rely on  
10 to extend studies post-introduction and to make the  
11 results of these studies public. Our members need  
12 this information and society is better off when data  
13 is continuously compiled and then made available.

14           In addition, because our members are above  
15 national compliance averages, we look closely at how  
16 they can maintain their health practice. We have  
17 found that a person must be logically and emotionally  
18 committed to managing disease, and they must believe  
19 their treatment protocols are right for them. Our  
20 members talk to us and it's our responsibility to  
21 bring their comments and stories to panels such as  
22 this one today.

1           But these are more than our members; these  
2   are our uncles and our aunts, our mothers and our  
3   fathers, our sisters, our boyfriends, our husbands and  
4   wives. So our responsibility today is large and it's  
5   up to me to convey their feelings in the three minutes  
6   I have remaining.

7           To quote one person, "all the women in my  
8   family have died from osteoporosis." A member from  
9   New Jersey told us yesterday on the phone, quote "I'm  
10   not yet post-menopausal, so I can't take any of these  
11   drugs, but I want the widest choice possible for when  
12   I can begin therapy." I quote, "I didn't know what  
13   osteoporosis was until I broke my hip 10 years ago."  
14   Said another member from Kansas City, Missouri, "I  
15   began to learn everything I could about options  
16   available and there weren't many. Today there are  
17   more. Tomorrow, I hope my daughter will have even  
18   better choices." Quote, "I work to supplement my  
19   Social Security and after my wrist fracture, I was  
20   unable to work as a cashier," says Ellen from  
21   Baltimore.

22           Ellen is 69 this year, and is back at work



1 but with limited range of motion in her wrists. She  
2 did not have a medical home at the time of her  
3 accident two years ago and was not on any bone  
4 strengthening medication. She is currently taking  
5 medication for her osteoporosis. Quote, "I wish I had  
6 paid attention to the medicine that was available,  
7 that could have helped prevent my broken wrist," she  
8 commented at an online patient event recently.

9           We know patients want choices and we know  
10 many patients are willing to do their homework so that  
11 they are well informed about their own osteoporosis.  
12 We also know that panels like this one are an  
13 important link between patients, physicians and  
14 medications. I hope I've been able to use my time  
15 efficiently today, and I hope I've represented our  
16 members throughout the United States by bringing their  
17 messages of a desire for new treatment options, a  
18 choice of how and when they take their drugs and how  
19 hard they are willing to work to make sure they stay  
20 informed, stay healthy, and stay active.

21           Thank you again, Madam Chairman, for the  
22 opportunity and for allowing the Global Healthy Living

1 Foundation and CreakyJoints to speak today. I look  
2 forward to working with you all in the future. Thank  
3 you.

4 DR. CARSON: Thank you.

5 Is Ellen Summers (ph) here?

6 Okay. Our last presentation, then, will be  
7 by Cynthia Pearson, Executive Director of National  
8 Women's Health.

9 MS. PEARSON: National Women's Health  
10 Network, thank you. I didn't receive any support for  
11 my travel here today. I'm local, and the organization  
12 I represent, National Women's Health Network, is a  
13 women's health consumer organization that's supported  
14 by contributions from thousands of individuals across  
15 the country and some foundation grants.

16 By choice, we don't accept any financial  
17 support from the medical industry. And I'm here to  
18 urge caution, which is very different from everything  
19 else you heard during the open public part of this  
20 meeting today. Everyone else has spoken either about  
21 the need for more awareness, the need for more  
22 treatment options, the need for more information. And

1 I think the fact that my urging caution seems  
2 contradictory to those other comments, is a reflection  
3 on the history of what's happened with osteoporosis in  
4 the United States over the last 25 years.

5 In my remarks, I'm going to concentrate --  
6 you have to answer questions about two very different  
7 populations -- about post-menopausal women and about  
8 cancer patients. I'm going to concentrate my remarks  
9 on post-menopausal women as fits our role as the  
10 Women's Health Network. If any committee member wants  
11 to ask me at the end of my remarks, I can say  
12 something brief about our reaction about cancer  
13 patients.

14 But to my point about what has been the  
15 history of the awareness of and the ability to  
16 adequately respond to women's needs for good treatment  
17 and support around osteoporosis. Well, I would say 25  
18 years ago, and probably many of the researchers who  
19 are here would vehemently agree, that at that time in  
20 the 1970s and the early 1980s, there was far too  
21 little awareness; that a combination of, I'll call it  
22 sexism and ageism, left many older women in painful

1 situations with vertebral crush fractures that were  
2 just thought to be -- they were told was part of old  
3 age, or with a hip fracture that hadn't been perceived  
4 as a risk in advance and wasn't prevented.

5           Thanks to many of the researchers who've  
6 been so active over a long time and caring clinicians  
7 and some voices from the women's health community,  
8 that's changed and we now have a time when there is  
9 more attention, more research, more diagnostic tools  
10 and more treatment alternatives, and that's a good  
11 thing.

12           I also want to acknowledge this sponsor's  
13 role as a new player in the world of osteoporosis  
14 treatment research, and in the very good job they did  
15 in including women of color, which is a step forward.  
16 Many previous trials haven't been as good on that.  
17 And by making a very special effort to get a high  
18 percent of women, 70 years and older, into their  
19 fracture trial to test their drug in the population  
20 for whom it could have potentially the most benefit.

21           But in addition to this good progress we've  
22 made at recognizing that osteoporosis is an important

1 public health concern for many older women, in our  
2 opinion, there has been over diagnosis, over treatment  
3 and unnecessary harm. So just two ways I want to  
4 illustrate that.

5           One is that the current FDA guidelines, as  
6 we all heard this morning, for testing a drug for use  
7 by healthy women to reduce their risk of fracture in  
8 the future, means that the guidelines only require  
9 evidence that the effectiveness of the drug is seen on  
10 x-ray; that a woman can come into this study with no  
11 symptoms, she can leave the study with no symptoms,  
12 and the FDA can find enough evidence of benefit to say  
13 that it works by their guidelines.

14           Current screening guidelines, which might be  
15 the entry for a woman into that study or after  
16 approval into the group for whom the drug could be  
17 prescribed as a preventive strategy-- current  
18 screening guidelines that are evidence-based are  
19 actually calling for screening for women starting at  
20 age 65. Those are from the U.S. Preventive Health  
21 Service Task Force.

22           Unfortunately, what we saw even here in this

1 room with our own public health agency, the FDA, is  
2 that there is a much too common impression created by  
3 very effective marketing campaigns that screening  
4 should start at age 50. So I went into those two  
5 things in some detail to just provide you the context  
6 that we see, that many women are getting screened who  
7 don't need it and that the FDA, who has to find some  
8 sort of guidelines for what studies they require, has  
9 guidelines that are so expansive that the question  
10 that was asked and not really answered this morning  
11 about how many women are needed to treat, the answer  
12 is pretty large.

13           With those rules for testing and the common  
14 misperception that screening should start at age 50,  
15 the number of women who need to be treated to get an  
16 effect and to see a benefit, to prevent one fracture  
17 that might -- even one fracture at all, but one  
18 fracture that might actually cause problems is pretty  
19 high. So if that number needed to treat is pretty  
20 high, then the safety questions become very important.

21           I'm seeing my sum up light, so I'll just sum  
22 up. As I heard this morning, listening to all the

1 presentations and as I read yesterday when I  
2 downloaded all the data that was online, we see an  
3 evidence of increased recurrence of breast cancer in  
4 cancer patients, increased occurrence of new cancers,  
5 including ovarian and cervical in post-menopausal  
6 women, increase of serious infections some of which  
7 required hospitalization. And both of these things,  
8 cancer and infection, are biologically plausible, as  
9 we heard -- as a cause and effect as we heard earlier  
10 this morning. And then there's the possibility of  
11 bone problems in the future.

12           So to really sum up, the FDA is going to ask  
13 you advisors at the end of the day to answer the  
14 questions that are attached to the agenda. And the  
15 questions go to, is there a reasonable expectation of  
16 benefit that outweighs the harm? And I would say  
17 looking at it from this perspective --

18           DR. CARSON: Thank you very much.

19           Thank you all for taking the time to prepare  
20 your comments, submit them, and of course, travel to  
21 present to us today. I'm always humbled by those who  
22 are willing to share the intimate details of their own

1 personal medical history for the benefit of everybody.

2           The open public hearing portion of this  
3 meeting has now concluded and we will no longer take  
4 comments from the audience. The committee will now  
5 turn its attention to address the task at hand, which  
6 is the careful consideration of the data before the  
7 committee as well as the public comments.

8           So let's go back to the question and answer  
9 session. I know we have a few left in the queue from  
10 before lunch.

11           Dr. Gut?

12           DR. GUT: Thank you very much, Dr. Carson.  
13 The sponsor conducted a really impressive development  
14 program with more than 30 clinical studies and more  
15 than 10,000 patients looking at efficacy and safety,  
16 but also pharmacokinetic and pharmacodynamics of  
17 denosumab. I'm interested in the safety profile in  
18 comparison in your two head-to-head Phase 3 trials  
19 with alendronate. So if you can please comment on the  
20 various events rates in those trials.

21           DR. EISENBERG: I'm sorry. I didn't quite  
22 hear the question. I apologize.



1 DR. GUT: Safety profile comparison in your  
2 two Phase 3 head-to-head trials with alendronate.

3 DR. EISENBERG: The alendronate comparison  
4 studies and the safety profile.

5 I think Dr. San Martin would be most  
6 appropriate to answer that since he conducted those  
7 studies.

8 DR. SAN MARTIN: As you said, we did two  
9 different comparison studies of denosumab versus  
10 alendronate. One was in the novel patients, 1,100  
11 patients were randomized to either receive denosumab  
12 or alendronate and followed for one year.

13 The other study was in patient previously  
14 treated with alendronate for about three years and  
15 then they switched to either continuing alendronate or  
16 received denosumab. Both studies were double-blind  
17 and there was no difference in any adverse event or  
18 serious adverse event that can be discriminated  
19 between alendronate and denosumab.

20 The primary endpoint was changed in bone  
21 mineral density of the hip and secondary endpoints of  
22 the spine, and in both endpoints, in both study there

1 was a significant improvement in bone mineral density  
2 that favored denosumab versus alendronate. In terms  
3 of safety, there was no difference in any AE or  
4 serious adverse event that were remarkable.

5 DR. GUT: Thank you very much.

6 DR. CARSON: Mr. Goozner?

7 MR. GOOZNER: Thank you. This gets to the  
8 summary of serious adverse events. At several points  
9 in the company's presentation, you said that they were  
10 roughly equal, and you gave some numbers. But I had  
11 some questions when I was reading the materials before  
12 today's meeting about Table 18 that was on Page 83 of  
13 the submission, where there were a number of serious  
14 adverse events that were listed there that included  
15 like femur fracture and femoral neck fracture.

16 I was just curious. Why are those added in  
17 under serious adverse events? Aren't those events  
18 related to treatment itself? In other words, the  
19 reduction in those events that we saw with denosumab,  
20 isn't that a result of treatment?

21 And so if we add those into the -- my  
22 question becomes, if we add those into the serious

1 adverse events, doesn't that sort of inflate the  
2 number that's on the -- or deflate the number that's  
3 on the denosumab side?

4 DR. EISENBERG: So let me see.

5 Do we have the table from the briefing book?  
6 We can bring that up.

7 But in terms of fracture endpoints, all  
8 fracture endpoints are captured in this study, so we  
9 don't discount any fracture endpoints whether they're  
10 reported as a serious adverse event from the fracture  
11 endpoint. So it wouldn't impact that. If we can  
12 bring the table up so I'm certain to answer your  
13 questions properly. Thank you.

14 So with respect to the question you've have  
15 raised, there were events that do get reported as  
16 serious adverse events, and that's based on the  
17 investigator reporting. So the process there is if  
18 the investigator reports this event as a serious  
19 adverse event for the reasons FDA highlighted, the  
20 patient would have been hospitalized obviously, we  
21 would capture that. But all fractures are captured in  
22 the endpoint, so you're just looking at two different

1 perspectives on this.

2 MR. GOOZNER: So what I want to do is I want  
3 to understand what is the difference in serious  
4 adverse events between placebo and drug. And so  
5 doesn't it make sense in creating that chart to back  
6 out the numbers that are drug related to the primary  
7 and secondary endpoints in the trial, so that I get a  
8 fair picture of other than drug related events.

9 DR. EISENBERG: I'm not sure I entirely  
10 understand the question.

11 MR. GOOZNER: In all honesty, I think the  
12 FDA did the same thing in their presentation, and I  
13 was very confused about this when I was reading it  
14 prior to the meeting, so I'm trying to get  
15 clarification now.

16 DR. CARSON: The standard way in which we --  
17 the FDA and all other pharmaceutical companies and  
18 academic institutions that capture adverse events is  
19 to display every adverse event and serious adverse  
20 event, regardless of whether they're at the endpoint  
21 of the study. Then when one analyzes not just the  
22 aggregate adverse events and serious adverse events,

1 one digs down into the variety of different terms in  
2 order to get an understanding of a variety of  
3 different adverse events that have been captured in  
4 the study, and that's what's been done here.

5 In fact, if we didn't actually capture those  
6 adverse events and serious adverse events of fracture,  
7 then we wouldn't be necessarily fully representing the  
8 safety profile. For example, if there was a  
9 therapeutic that actually increased your risk of  
10 fracture, then you would want to be able to capture in  
11 your adverse event database.

12 MR. EISEMBERG: In thinking about your  
13 question, I understand your confusion. So I think I  
14 understand it and it's actually a standard way in  
15 which we approach assessing for an adverse drug  
16 reaction, is what I think you're thinking about. And  
17 that assessment is to look at adverse events that  
18 occur in placebo versus your treatment, and then to  
19 say if it -- and the standard way of approaching is to  
20 say if it occurs in 1 percent more of your treated  
21 patients than your non-treated patients, that might be  
22 a real adverse event, or if there is a medical reason

1 based on causality or an unusual number of events to  
2 pay attention to it, then you assume that that's a  
3 drug related event. And we do those analyses of  
4 adverse drug reactions. And I don't know if we  
5 have -- we didn't present that in that way today. You  
6 saw all the data for both arms.

7 I can tell you the adverse drug reactions  
8 that I highlighted as those observed; so eczema,  
9 cataracts, and several infections of adverse events.  
10 infectious terms, the bacterial infections, UTI, the  
11 diverticulitis we commented on -- those events were of  
12 greater frequency in the denosumab treated patients  
13 than the placebo patients.

14 So we would consider those, as we've  
15 highlighted -- if we bring the slide up, 87, and I've  
16 highlighted those, the skin infection, latent  
17 hospitalization, hypocalcemia. Clearly, each one of  
18 these events we would consider from a  
19 pharmacovigilance safety perspective to be an adverse  
20 drug reaction, which I think is what you're asking.  
21 I'm not sure if I've gotten your question answered  
22 yet, but I think that is what you're asking.

1           MR. GOOZNER: I think that gets to it. I'm  
2 trying to in my own mind create what serious adverse  
3 events are drug related and what are specific, as  
4 opposed to a global score that sort of balances the  
5 two and says that they're about equal, placebo versus  
6 drug, when in fact, a lot of the adverse events were  
7 actually caused by the drug being effective.

8           DR. EISENBERG: Again, causality, just to be  
9 clear, we take a -- since we never really know  
10 causality unless there's a very clear understanding of  
11 mechanism, we actually don't bias our assessment by  
12 making a decision as to whether an adverse drug  
13 reaction is causal or not.

14           So for example, with cataracts, we consider  
15 that an adverse drug reaction because the numbers are  
16 different.

17           Do we have an explanation? No. Could it be  
18 due to chance? Yes. But we still would list that.  
19 We still believe that would be an adverse drug  
20 reaction. So causality is not an underpinning of  
21 making that determination. We simply objectively look  
22 at the differences. And what I highlighted for you in

1 the slide are those events that are objectively  
2 different between the two groups.

3 DR. CARSON: Thank you.

4 Dr. Collins?

5 DR. COLLINS: I just wanted to reiterate, I  
6 think that this degree of suppression that we see both  
7 in terms of bone markers and on histomorphometry, I  
8 remain pretty concerned that this is really a signal  
9 of long-term problems, as you do. And it's reassuring  
10 to know that you have studies in place that will pick  
11 up on this. And we did hear though that already in  
12 other studies with this drug, in cancer patients, that  
13 some cases of osteonecrosis of the jaw have begun to  
14 appear.

15 Any subtrochanteric fractures either in this  
16 study or the cancer studies?

17 DR. EISENBERG: There were three in the  
18 placebo group. That's the only cases that we have.

19 DR. COLLINS: So then in terms of the  
20 long-term follow-up studies, that if these do begin to  
21 appear, and I don't know if this is a question for you  
22 or for the FDA, what are the sort of criteria for a



1 sort of exit strategy of what will signal a real  
2 concern about this, and what actions will be taken in  
3 regard to this?

4 DR. EISENBERG: Well I can comment briefly  
5 as to how we've thought about the long-term safety  
6 assessment. We will be acquiring data in a broad  
7 number of studies as well as the other  
8 pharmacovigilance studies. We communicate this  
9 information on a regular basis. So safety updates,  
10 for example, that are comprehensive are provided to  
11 regulators more frequently when a drug is first  
12 approved and at least annually thereafter.

13 Any of the studies that we commit to that  
14 have endpoints get recorded as soon as those data are  
15 available, and we make those data available  
16 immediately. I think one of the aspects that's unique  
17 to denosumab is should we see a signal or should there  
18 even be a concern in an individual patient to the  
19 signal, it is reversible.

20 DR. COLLINS: Right. And that's very  
21 comforting, which isn't the case with the  
22 biphosphonates. But one of the things I wonder too --

1 I mean, is really this degree of suppression really  
2 necessary to get the effect that you want? Could less  
3 frequent dosing or a lower dose achieve the same  
4 protection with a lower risk of some of these things  
5 we're talking about, ONJ, et cetera?

6 DR. EISENBERG: If you'd like, we could walk  
7 through the data in detail. I can tell at a high  
8 level that in most of what you see in terms of the  
9 pharmacodynamic profile of denosumab is that all of  
10 the doses that we looked at in our Phase 2 studies  
11 suppressed the markers immediately. Much of the  
12 difference really relates to how long a period you  
13 want to have between the doses. So the six-month  
14 dosing interval was selected based on a dosing  
15 interval that was felt to be both convenient. And,  
16 also, at the end of the interval we actually saw some  
17 slight increase in the CTX marker, suggesting it  
18 wasn't an over suppression effect.

19 So six months was selected that way. We're  
20 happy to walk through, if you'd like to look at the  
21 data at shorter dosing intervals, but that's the basic  
22 rationale.

1 DR. ROSEN: Could you walk through the  
2 Phase 2 on that point for us, because I'm a little  
3 confused about why you selected 60 milligrams every  
4 six months versus the 14 milligrams that gave the  
5 increase in spine bone density in the Phase 2 dose  
6 ranging study.

7 DR. EISENBERG: Let me have Dr.  
8 Stehman-Breen comment on that.

9 DR. STEHMAN-BREEN: So the goal in  
10 identifying the dose was to be able to provide the  
11 lowest dose with the maximal increase in bone mineral  
12 density that could be given at the least frequent  
13 dosing interval. And as you've probably noticed from  
14 your briefing document, we assess a large number of  
15 different doses and two different dosing frequencies.

16 It was, as you can imagine, a very  
17 significant decision in terms of choosing the dose.  
18 And so let me walk you through a little bit of data to  
19 help you understand a little bit better what our  
20 rationale was.

21 So these are some data from the Phase 2  
22 study. And on the left side of the figure, you can

1    see the mean CTX values, which are on the percent  
2    change from baseline, is on the vertical axis with  
3    time on the horizontal axis.

4               What you can see is that the 30 every three  
5    months, the 60 every six months, and the hundred-and-  
6    two-ten every six months had generally the same levels  
7    of suppression of CTX with a little bit of attenuation  
8    at the dosing interval with 60 milligrams every six  
9    months. The 14 milligrams every six month dose didn't  
10   appear to have adequate suppression of CTX.

11              DR. EMERSON: This graph doesn't include the  
12   14 milligrams every three months.

13              DR. STEHMAN-BREEN: I promise I'll get there  
14   in a minute, Dr. Emerson.

15              DR. EMERSON: Okay.

16              DR. STEHMAN-BREEN: So if you look at the  
17   right side of the figure, you can see bone mineral  
18   densities, and these were --

19              DR. EMERSON: Can I just interrupt for a  
20   second --

21              DR. STEHMAN-BREEN: Sure.

22              DR. EMERSON: -- and ask you, when you say

1 not adequate suppression, what are you referring to?  
2 Because it states 14 every six months, it goes down to  
3 80 percent and then comes up 40 percent suppression.  
4 So what's your definition of adequate suppression?

5 DR. STEHMAN-BREEN: So that's a great  
6 observation. As Dr. Eisenberg pointed out, all of the  
7 doses result in the same maximal level of suppression  
8 and the difference is really the duration of that  
9 suppression.

10 Now if you look on the right side of the  
11 figure, you can see the percent change in baseline and  
12 bone mineral density and you can see that that  
13 14 milligrams every six month dose did not provide  
14 significant increases in bone mineral density, as  
15 highlighted by the white dot, as the other doses did.

16 DR. EMERSON: But that's hip. That's not  
17 spine, that's hip, right?

18 DR. STEHMAN-BREEN: That's hip.

19 DR. EMERSON: But spine was four-and-a-half.

20 DR. STEHMAN-BREEN: Yeah. So I'm going to  
21 show you some more data in just a minute. And again,  
22 as you can imagine, there was a tremendous amount of

1 information that needed to be digested in making this  
2 decision.

3           These are the bone mineral density changes  
4 at 24 months for all of the doses that we assessed.  
5 And I know it's a bit of a complex figure, but if you  
6 focus on the 14 milligrams every three month dose,  
7 which is in grey, and the 60 milligram every six month  
8 dose that's in yellow, you can see that there are some  
9 differences depending on where you measure, the lumbar  
10 spine, the total hip, or the trochanter. And when we  
11 assess the totality of the data, the 60 milligrams  
12 every six month dose appeared to have greater  
13 increases in bone mineral density and we could use it  
14 at a less frequent dose interval.

15           And importantly, it had that slight  
16 attenuation at the end of the dosing interval, which  
17 was felt to be a desirable effect with a little bit of  
18 a release or return of osteoclast function at the end  
19 of the dosing interval.

20           So we were balancing two things here. We  
21 were balancing not having over suppression without  
22 having too much release of osteoclast function, which

1 one might be concerned that there would be over  
2 activity of the osteoclasts with potential adverse  
3 events related to that.

4           So this dose provided the greatest balance  
5 of increases in bone mineral density, but again  
6 allowing a little bit of release at the end of the  
7 dosing interval and allowing that six month dosing  
8 interval, which was felt to potentially help with  
9 adherence of the drug, which as you heard from  
10 Dr. Siris, is an important problem in osteoporosis.

11           Did that answer the question?

12           DR. CARSON: Dr. Emerson, are you happy with  
13 the answer?

14           DR. EMERSON: Well, if you look at that last  
15 graph and you look at the six milligrams every three  
16 months, that's also looking fairly good. And so I  
17 think the statements that it's clear that this is the  
18 lowest dose is not there. Although I do wonder at the  
19 sort of vacation idea, that by having the high dose,  
20 whether you're effectively giving the patients a  
21 vacation from the drug for a little while and still  
22 getting the bone mineral density, but I can imagine

1     that would be beneficial.

2                 DR. CARSON:   Dr. Rosen?

3                 DR. ROSEN:   I think it's very hard,  
4     retrospectively, to go back and say you picked the  
5     right dose, so therefore you picked the right dose.  
6     And it's very hard for us to second-guess that.  I  
7     mean, obviously, there were a number of things that  
8     went into that sort of decision-making.  But I am  
9     surprised a bit that the lowest optimal dose actually  
10    is significantly lower.

11                DR. CARSON:   Dr. Nelson?

12                DR. NELSON:   Yeah, I had questions about the  
13    over suppression also.

14                What's the longest you've had any patients  
15    on this?

16                DR. STEHMAN-BREEN:  We have subjects that  
17    have been on denosumab for more than six years, that  
18    were part of our Phase 2 study.

19                DR. NELSON:   And is there a plateau in the  
20    bone density accrual or is it just keeps going up?

21                DR. STEHMAN-BREEN:  No, there isn't, and if  
22    we can bring up that slide, you'll see that there are



1 continued increases in bone mineral densities out to  
2 72 months. And that's illustrated by the yellow  
3 dotted line here.

4 DR. NELSON: And I also had a question about  
5 the holiday period. It seems to me like it would be  
6 quite beneficial because you have a perfect setup here  
7 where you have a recovery over a short time frame. So  
8 have you looked specifically at what are the effects  
9 of holidays in terms of accruing bone density? And is  
10 there maybe a better paradigm here for taking  
11 advantage of both sides of this equation?

12 DR. STEHMAN-BREEN: Well, we feel that what  
13 we tested is the data that I've shown; what we've  
14 assessed in clinical trials. And we haven't assessed,  
15 for example, longer dosing intervals. But again, this  
16 is a balance between the right level of suppression  
17 without what there has been identified as an area of  
18 observation or an area of concern, which is too much  
19 release at the end of the dosing interval, where you'd  
20 have suppression of bone turnover followed by a robust  
21 increase in osteoclast function.

22 So in balancing that, we've ultimately ended

1 up with a dose that provides significant reductions in  
2 bone turnover at the beginning of the dosing interval  
3 and then, again, some release at the end of the dosing  
4 interval. And with our three years of fracture data,  
5 in addition to the prostate cancer study with hormone  
6 ablation therapy, has demonstrated very robust  
7 reductions in fracture risk.

8 Now as was pointed out, we've very committed  
9 to continuing to understand our long-term safety  
10 profile and we feel that we can effectively do that  
11 with our large extension study in addition to the  
12 variety of other studies that Dr. Eisenberg outlined  
13 and our large set of observational studies.

14 DR. CARSON: Okay.

15 Dr. Gulley?

16 DR. GULLEY: Yes, thank you. So my question  
17 was regarding the 138 Study, the prostate cancer. So  
18 realizing that this is a heterogeneous patient  
19 population with biochemical failure on hormonal  
20 therapy, the one slide that was looking at the  
21 assessment of PSA antigen -- I believe slide 60 --  
22 that slide seemed to show no difference between the

1 two groups. But was there any another look at PSAs in  
2 terms of either PSA velocity, PSA doubling time, time  
3 to castration resistance that was looked at in this  
4 study to help us understand perhaps differences in  
5 progression?

6 DR. EISENBERG: Well let me ask Dr. Matthew  
7 Smith, who was the principal investigator of that  
8 study, to comment and maybe we could bring up slide 60  
9 so that that's available for comment.

10 DR. SMITH: So I'm Matthew Smith, a prostate  
11 medical oncologist from Massachusetts General Hospital  
12 and the P.I. for the prostate HALT study. So I think  
13 what you're raising is the issue of sort of potential  
14 concern about that this therapy would impact  
15 underlying cancer control. The study had  
16 pre-specified ways to look at this. There are three  
17 ways. One is PSA progression, one is bone scan  
18 progression, and the other is overall survival. And  
19 really, by all of those metrics, there is no signal to  
20 suggest greater cancer progression.

21 So you see that one way here, which is  
22 looking at really -- this effectively is showing in

1 the slide there, the time to progression to castration  
2 resistance. Because what we're looking at here in the  
3 bar graphs is the proportion of patients who meet  
4 those PSA metrics despite a castrate level of  
5 testosterone.

6           So I think what you can appreciate there is  
7 there's really no suggestion using early sensitive PSA  
8 criteria of greater cancer progression. So we find  
9 that quite comforting.

10           Dr. Kehoe nicely pointed out -- though that  
11 as you'd expect in a population of hormone sensitive  
12 patients, there were very few deaths, as you again  
13 would expect in this favorable population. We  
14 actually believe that the drug may in fact, delay or  
15 prevent of the development of metastatic disease to  
16 bone. And we're testing that hypothesis in a  
17 population of high risk patients with castration  
18 resistant disease.

19           DR. GULLEY: And just as a follow up, there  
20 was very few number of patients that had actual  
21 metastatic disease to bone.

22           Is that correct?

1           DR. SMITH: Right. So again, three ways we  
2 looked. The PSA, which would be -- and as most of the  
3 audience would know, PSA while it has its  
4 controversies in screening, is a very reliable marker  
5 of cancer progression. So uniformly, patients would  
6 progress by PSA before developing radiographic or  
7 clinical progression. So in this study, in a  
8 pre-specified manner, we also looked at bone scan  
9 progression and there are no discernible differences.  
10 Although again, the rates of significant bone scan  
11 abnormalities was only about 5 percent at three years  
12 on both groups.

13           DR. CARSON: You may as well just stay up  
14 there because I also had -- are you sure that the PSA  
15 is as predictive of the spread of disease in a  
16 population treated with monoclonal antibodies, as it  
17 is in one who's not treated with biological products?

18           DR. SMITH: Well the specificity of the  
19 antibody would -- if your question would be the  
20 concern that it would interfere with PSA measurement,  
21 I believe there's absolutely no concern about that.  
22 Perhaps someone else could address that.

1 DR. CARSON: Not measurement, but rather  
2 release or change in the biologic -- I mean is it as  
3 predictive in that?

4 DR. SMITH: Well, again, we're not relying  
5 solely on PSA here. So to answer your question, I  
6 don't know how you would know except by doing the  
7 clinical trial. So I think there's supportive data,  
8 not just PSA, although again, that would be earliest  
9 and most sensitive indication of disease progression.  
10 There's absolutely no detrimental effect on bone scan  
11 progression at three years. And as you saw in slide  
12 61, overall survival was -- there's absolute  
13 similarity of overall survival.

14 DR. CARSON: The second question that I had  
15 was, were those patients who developed cataracts  
16 treated differently for their prostate cancer than  
17 those patients who did not develop cataracts?

18 DR. EISENBERG: We looked at the cataract  
19 factors, patient related factors. We honestly can't  
20 find anything that gives us any comfort that we  
21 understand the signal.

22 DR. CARSON: Dr. Uzel?

1 DR. UZEL: Hi. My question is regarding the  
2 infections that led to SAEs.

3 Did any of those patients who had life-  
4 threatening infections or serious infections were also  
5 on disease modifying agents or other immunomodulatory  
6 drugs given this patient population, or were they  
7 neutropenic? Are there any other co-morbidities or  
8 other factors that may have led to these infections?

9 DR. EISENBERG: I don't think if we look  
10 across the serious infections, maybe Dr. Stehman-Breen  
11 will comment, that in the totality of all infections,  
12 that we saw any factors that we would consider  
13 confounding in terms of other treatments. And as we  
14 noted, certainly the opportunistic infections, viral  
15 infections that typically would be associated with  
16 those kind of immune modifying drugs were actually  
17 more frequent, was no difference between the two  
18 groups I guess is the fairest way to state it.

19 DR. UZEL: My second question is I  
20 understand the data about the immunogenicity of this  
21 drug and it's predicted to be very little in the  
22 future, but if patients or the physicians report to

1    you a significant concern about immunogenicity, will  
2    you be able to provide assay or help these physicians,  
3    patients to detect if there's any other antibody  
4    formation?

5               DR. EISENBERG:  Oh, absolutely.  Amgen has  
6    actually a very significant effort to ensure that if  
7    antibodies develop, we can provide assays and  
8    determine whether they're neutralizing and provide  
9    additional information?

10              DR. UZEL:  Thanks.

11              DR. CARSON:  Dr. Buzdar?

12              DR. BUZDAR:  Yeah, the question which I have  
13    is that here the indication, which is being sought, is  
14    for treatment of osteoporosis, prevention of  
15    osteoporosis and patients who are cancer therapy  
16    getting therapies which are affecting the bone  
17    turnover, slowing that down.  And on the downside when  
18    we look at it, that it does increase the risk of  
19    developing some cancers, at least there is some hint  
20    of it, some hint of causing increased infection, some  
21    hint of causing the other serious side effects.

22              Question is, have you looked at it or



1 developed some kind of a model in which you can  
2 predict that in the overall therapy, the ratio will be  
3 favorable? That i.e., preventing a major life  
4 changing event like a fracture of the hip versus  
5 developing a lung cancer or a breast cancer or an  
6 ovarian cancer, which is also a major life changing  
7 event and far more lethal than a hip fracture.

8 DR. EISENBERG: Well certainly -- I mean,  
9 part of this is what the level of incidence is. So I  
10 think, first, if you start to look at how you weigh  
11 small differences that don't reach statistical  
12 significance, I'd remind you to start that the overall  
13 benefit in terms of survival actually favors  
14 denosumab. If we then ask the question of the number  
15 of fractures, absolute number of fractures that  
16 occurred, that signal is quite strong.

17 Now can I tell you from the percentage of  
18 patients who have a hip fracture, how many lives we  
19 would save; no, I think that would be presumptuous,  
20 though the number of fractures that are prevented and  
21 the number needed to treat to prevent those fractures  
22 is actually quite low, and my recollection is

1 somewhere around one in 30 would be patients  
2 treatable -- will be prevented from having a fracture.

3 Now if you then ask the question -- again,  
4 keeping in mind that if you look overall when we do  
5 these number needed to treat, number needed to harm,  
6 we usually don't look at statistically insignificant  
7 differences on the harm side. We look at data that  
8 are confirmed.

9 So I think your point is fair that there are  
10 potentially risks that we have to monitor long-term,  
11 but none of those have been confirmed. Some cancers  
12 were actually less with denosumab treatment. And so I  
13 think it's a little difficult for me to answer that  
14 question with respect to an absolute risk, since one  
15 has not been demonstrated in that regard. I think in  
16 terms of the skin infection risk, we have a little  
17 more concern. But most of the other risks don't  
18 reach -- none of them reach statistical significance.  
19 None of them are more than small differences.

20 DR. BUZDAR: Yeah, but I'm not concerned  
21 about skin infection, which is easily treatable. I am  
22 more concerned about ovarian cancer, which is almost

1 numerically is doubled.

2 DR. EISENBERG: That's a fair point and --

3 DR. BUZDAR: Because the thing is, that is  
4 life threatening, potentially lethal disease, almost  
5 in majority of patients. So the thing is we can't say  
6 that, oh, we will see how the data evolves in the data  
7 there too. I think this data, if somebody wants to  
8 sit and think about it, should be able to calculate  
9 what is the net benefit taking into account.

10 Because the thing is, if you're trying to  
11 expose a huge number of patient population to a  
12 therapy which is increasing, even a small but subtle  
13 increase in potentially life changing events, you have  
14 to calculate what is the therapeutic index of the  
15 therapy in the long run?

16 DR. EISENBERG: Did you want to say  
17 something to that?

18 The only comment I'd make is, one, that it  
19 is has to be confirmed. So ovarian cancer actually  
20 was one that since we were quite interested in  
21 reviewing the safety, I reviewed and compared to other  
22 trials, a comparable trial. Just to give you a

1 perspective on this, our estimates and malignancy  
2 rates in trials are rarely very exact.

3           So for example, the RUTH trial with  
4 raloxifene, which is very large, similar patient  
5 population, 10,000 patients, 10,000 women treated with  
6 raloxifene or placebo, so placebo controlled. Not a  
7 fracture trial. There were excesses both in  
8 endometrial and ovarian cancers in small numbers. I  
9 highlight that only because the integrated safety  
10 databases for raloxifene are very clear. There is no  
11 risk.

12           So when we're looking at small numbers, to  
13 count nine versus five in an isolated sample set  
14 really doesn't provide an absolute estimate of risk.  
15 I think we should restrict our estimates of risk to  
16 what's statistically significant and demonstrated in  
17 the data we're showing you.

18           DR. CARSON: Dr. Margolis?

19           DR. MARGOLIS: Thank you. I just have a  
20 quick clarification of a slide that Dr. Eisenberg  
21 showed near the end. You were talking about a safety  
22 study of 380,000 individuals and then showed a slide

1 looking at two databases, one of which is a medical  
2 records database of 120,000 and 160,000 individuals.

3 Did you mean that you're going to do a study  
4 yourself, de novo, or are you going to have a  
5 prospective cohort study of 380,000 individuals that  
6 you're enrolling, or are you going to do a bunch of  
7 database studies that in total have observations on as  
8 many as 380,000 individuals?

9 DR. EISENBERG: No. Our intent obviously  
10 since we have the advantage that when  
11 denosumab -- assuming denosumab's approved and enters  
12 into the market, we can get a de novo cohort, is to  
13 accrue a de novo cohort. And we base those numbers on  
14 the number of women in those databases who have post-  
15 menopausal osteoporosis are treated with other  
16 therapies.

17 Then a very conservative assumption, that  
18 somewhere in the order of 5 percent -- or 10 percent  
19 of patients who are currently treated might be treated  
20 with denosumab, and then an accrual time of five or  
21 six years.

22 But the number is based on a prospectively

1 defined cohort to allow an assessment of risk as low  
2 as one in 100,000.

3 DR. MARGOLIS: I'm still confused. So it's  
4 380,000 people that will be in a cohort that's  
5 represented within those data sets; not a cohort where  
6 you're deciding what data you're collecting. You're  
7 deciding what other tests you're doing. It's a  
8 prospective --

9 DR. EISENBERG: It's within the -- yes,  
10 absolutely. We would look to --

11 DR. MARGOLIS: It's within those other  
12 studies. Other people would be determining reason to  
13 treat.

14 DR. EISENBERG: Right.

15 DR. MARGOLIS: What follow ups they're going  
16 to do.

17 DR. EISENBERG: Exactly. It's the standard  
18 approach, yes.

19 DR. MARGOLIS: Okay.

20 DR. CARSON: Thank you.

21 Let me also remind the panel that we will  
22 have time to discuss, so let's just try to get the

1 information that you feel is missing from the sponsor.

2 Dr. Johnson?

3 DR. JOHNSON: Thank you. Because we're  
4 being asked to look at specific indications and being  
5 asked questions in regards to them, looking at your  
6 HALT study in women with breast cancer, can you give  
7 me some information on the sample number that was  
8 chosen? Because it's significantly less than we see  
9 certainly in the prostate study, and certainly many  
10 less than in the PMO study.

11 Also, the length of time for that study, I  
12 think it was limited initially to two years and that's  
13 all the data that we have. I know you're extending it  
14 out, but it seems like this is somewhat smaller and  
15 shorter than your previous studies.

16 Can you explain this?

17 DR. EISENBERG: Certainly. The design of  
18 that study, as I highlighted actually in my opening  
19 comments, was specifically powered to look at bone  
20 mineral density. Since, as FDA highlighted, once a  
21 novel agent that improves bone mineral density and  
22 bone strength has been demonstrated to reduce

1 fractures, then it's considered confirmatory to look  
2 at bone mineral density in subsequent studies. So  
3 both the prevention breast cancer study and the  
4 prevention HALT study actually are similarly sized.

5           Now we did have a different approach in the  
6 study in men, and the reason for that is simple.  
7 There are no large-scale studies of osteoporosis  
8 treatment or bone loss treatment in men. So the  
9 rationale there, really in collaboration with  
10 Dr. Smith and others was, let's do a study in that  
11 population which really has never been studied to the  
12 extent that women with post-menopausal osteoporosis  
13 and bone loss have been studied, that's sufficiently  
14 large to allow a secondary endpoint of fracture  
15 prevention. That's the rationale.

16           DR. CARSON: Dr. Richardson?

17           DR. RICHARDSON: The preamble to the  
18 applicant's information talked about some of the other  
19 factors that are important in bone health, including  
20 some of the lifestyle influences, smoking, diet,  
21 exercise, alcohol intake. And it would be great  
22 someday to see just what those have as an impact on



1 bone mineral density.

2 I understand the numbers are not thought to  
3 be particularly reliable in the studies that have been  
4 done, but these things obviously vary a great deal  
5 around the globe also. And I'm curious whether you  
6 stratified for any of these factors in your studies?

7 DR. EISENBERG: We didn't stratify.

8 I don't know, Dr. San Martin, if you have  
9 any comment.

10 Just sort of background demographics, I  
11 think we're very balanced with respect to all those  
12 factors, I don't know -- the smoking and other things  
13 that we would have highlighted.

14 DR. RICHARDSON: You mean you collected the  
15 information?

16 DR. EISENBERG: Yes, we collect that  
17 information, much of it.

18 DR. SAN MARTIN: We did collect all the  
19 information that is used to score the patients using  
20 the FRAX tool, and we stratify by age, which is a more  
21 important risk factor for fracture. And the bone  
22 mineral density increase is very similar across all

1 the baseline categories you mentioned.

2 DR. RICHARDSON: Well then maybe you could  
3 tell me how the randomization was carried out. Was  
4 this done in a central office where as these patients  
5 were entered, they were randomized at that time, or  
6 were they randomized within countries?

7 I mean they're -- for example, the smoking  
8 rates vary a great deal from country to country.  
9 Eastern Europe has very high smoking rates these days.  
10 How was that randomization done?

11 DR. EISENBERG: Let me ask the principal  
12 investigator of the study. Dr. Cummings can perhaps  
13 comment if he's -- or actually Steve Snappin, the  
14 statistician, can comment on randomization.

15 DR. RICHARDSON: My point with this is, is  
16 there a reason that the placebo arm had more lung  
17 cancers and more fractures? I mean did you have more  
18 smokers randomized to the placebo arm, for example?

19 DR. EISENBERG: I'll ask Dr. Snappin to  
20 comment. He's the statistician who's been involved in  
21 analysis.

22 DR. SNAPPIN: Steve Snappin from

1 Biostatistics. I can just comment on how the  
2 randomization was done. It was a central  
3 randomization system using an IVRS, or interactive  
4 voice response system, stratified only by age  
5 category. So four age categories, and the women were  
6 randomly assigned treatment groups within each of the  
7 four age categories.

8 DR. RICHARDSON: So the answer is, no, you  
9 don't know.

10 DR. EISENBERG: All the factors appear  
11 completely balanced between the two groups as far as  
12 we can tell.

13 DR. RICHARDSON: No, you don't know, it  
14 sounds like.

15 DR. EISENBERG: No, we do know.

16 DR. CARSON: Did you look at the various  
17 factors, lifestyle factors, mentioned between those  
18 two groups after stratification or after  
19 randomization?

20 DR. STEHMAN-BREEN: So randomization was  
21 quite effective and all of the factors you outlined  
22 were balanced across groups. The lower incidence of

1 lung cancer that was observed in the denosumab group,  
2 we have attributed it to chance. And again, it's not  
3 unexpected that in a randomized trial, you would have  
4 small numerical imbalances in certain types of  
5 cancers.

6 In this study we had numerical imbalances  
7 that favor denosumab in lung cancer; malignant  
8 melanoma, that were as large as the imbalances that we  
9 saw for example with ovarian cancer. This is very  
10 typical of a randomized trial, even of this size.

11 DR. SAN MARTIN: I guess the other piece of  
12 information that may help is that the randomization  
13 blocks were four, so that takes care of any type of  
14 imbalance by region. So it's unlikely to see any  
15 imbalance.

16 DR. CARSON: Dr. Richardson, any other  
17 questions?

18 DR. RICHARDSON: No, thanks.

19 DR. CARSON: Dr. Emerson?

20 DR. EMERSON: Just to follow up a little bit  
21 on maybe what can seem like our preoccupation with  
22 these risks that, as you say, are not statistically

1     significant. But statistics means never to have  
2     you're certain and it's what we're scared off. But  
3     you made reference to a number needed to treat.

4             Can you elaborate upon that?

5             DR. EISENBERG: Sure.

6             DR. EMERSON: Both in terms of the treatment  
7     of osteoporosis and the prevention.

8             DR. EISENBERG: Yes, we can. I have a slide  
9     in terms of number needed to treat.

10            This is for the treatment indication. This  
11     simply shows you the difference, as you'd expect,  
12     based on the absolute rates, so for each of the  
13     fractures, the pre-specified and other fractures.

14            Also, we identified the higher risk  
15     patients, older patients, and clearly since they're at  
16     higher risk of hip fracture, that tends to be over  
17     weighted in terms of bringing you down to a smaller  
18     number. I believe actually in response to your --

19            DR. EMERSON: And this is osteoporosis?

20            DR. EISENBERG: This is osteoporosis.

21            DR. EMERSON: And this is treatment --

22            DR. EISENBERG: Treatment. And then in

1 response to your question before the break,  
2 Dr. Snappin, I think you went and calculated the data  
3 for prevention, right?

4 DR. SNAPPIN: Yeah. So just to clarify on  
5 the numbers that were just on the screen, that refers  
6 to the numbers of women treated for three years, the  
7 duration of the trial. And just to give a rough  
8 sense, you asked a question earlier in the morning  
9 about cohort of women at somewhat lower risk, let's  
10 say. And I think the example was at a risk of 15 per  
11 1,000 per year. And what would be the number needed  
12 to treat in that case.

13 Obviously, we can't answer directly because  
14 we haven't done the study, but you can get I think a  
15 sense of what the numbers needed to treat would be.  
16 If you imagine that if the rate is 15 per thousand,  
17 the drug effect is something like a prevention of two  
18 thirds of the events, meaning 10 per 1,000 would be  
19 prevented in on year. Over three years to correspond  
20 to the duration of the trials that we did, that would  
21 be 30 per 1,000, resulting in and NNT of about 33,  
22 just as a rough guess.

1 DR. EMERSON: For any fracture, a 33? Just  
2 because this is going to figure in, just to make  
3 certain it agrees, I also find for prostate cancer, I  
4 agree with your numbers that you just put up there and  
5 I come up with about 50 needed to treat for the  
6 prostate cancer. Would that be --

7 DR. SNAPPIN: Correct. We calculated  
8 something in the forties, correct?

9 DR. EISENBERG: And I think it's important  
10 because when I calculated that number, I also looked  
11 at the population, and it is a low risk in mixed  
12 population. And Dr. Smith can certainly comment. So  
13 it wasn't a population necessarily picked for a high  
14 risk of fracture for prostate.

15 DR. EMERSON: And another real quick  
16 question is, that's any fracture. And so we've got a  
17 whole lot of fractures, and you're picking out -- some  
18 of the definition of your fractures are quite  
19 subclinical. So in terms of your vertebral fractures  
20 of looking for an increase in the amount of existing  
21 fracture, you call it a new fracture.

22 Do we have a feel for -- the hip fracture is

1 clearly significant, clinically, but --.

2 DR. EISENBERG: I mean the pre-specified  
3 endpoint is the most robust obviously because of  
4 ascertainment and predefined criteria.

5 But Dr. Stehman-Breen, you may want to  
6 comment in terms of other fractures. Many are  
7 symptomatic in terms of vertebral fractures.

8 DR. STEHMAN-BREEN: Yes. Vertebral  
9 fractures are often asymptomatic in that women don't  
10 realize they've had those fractures. But over time,  
11 they really do contribute -- as we've heard from one  
12 of public speakers and others, they contribute to a  
13 significant amount of morbidity in women as they get  
14 older.

15 DR. CARSON: Mr. Goozner?

16 MR. GOOZNER: I was actually going to ask  
17 about the number needed to treat, and they've answered  
18 the question. I would only just add that, that slide  
19 that you just threw up there should have been in the  
20 original briefing materials, in my humble opinion.

21 DR. CARSON: Dr. Rosen?

22 DR. ROSEN: Yeah, I'd like to revisit NNT



1 for the prevention arm.

2           So you're telling me that you can't  
3 really -- the number of fractures in the prevention  
4 arm was relatively low. I think there were six in one  
5 arm and -- so you're telling me that the NNT for these  
6 low risk individuals was 33 for the denosumab treated  
7 individuals?

8           DR. SNAPPIN: No, this --

9           DR. ROSEN: Yeah, you can't say that, right?

10          DR. SNAPPIN: Cannot say that.

11          DR. ROSEN: You cannot say that. We need to  
12 clarify that.

13          DR. SNAPPIN: Correct. We were talking  
14 hypothetically about a population with a risk of 15  
15 per 1,000.

16          DR. ROSEN: Right. But that may clearly not  
17 be the case, since the T-score is minus 1.5 and these  
18 individuals were not high risk individuals. I wanted  
19 to ask the group -- incidentally, I thought the  
20 presentation was excellent. And I'm not trying to be  
21 critical, but I'm trying to explore things that are  
22 important for this committee.

1           I wanted to ask the group -- and maybe  
2   Dr. Cummings can comment on this.

3           The fracture risk reduction in the non-  
4   vertebral fractures was 20 percent with denosumab, and  
5   that's with a hip bone density that's much higher than  
6   what you see with other treatments, and clearly spine  
7   bone density much higher. And that's about where the  
8   newer data look like in terms of meta-analysis.

9           So if a lot of what you're basing your  
10   studies on are change in BMD, why are you only getting  
11   about the same risk reduction as you would with every  
12   other treatment that we have available?

13           DR. EISENBERG: Yeah, I think Dr. Cummings  
14   would like to respond --

15           DR. CUMMINGS: Dr. Steve Cummings. I was  
16   principal investigator and leader of the Steering  
17   Committee for the Freedom trial, and Professor of  
18   Medicine, Epidemiology and Biostatistics Emeritus at  
19   the University of California, San Francisco.

20           As you know, yes, the meta-analyses suggest  
21   that virtually all antiresorptive drugs have about a  
22   20-25 percent reduction in non-vertebral fractures.

1 And that degree of reduction might be a little less in  
2 populations that have somewhat lower risk. And so  
3 that would fit the picture here, but I think that it's  
4 well within the range of non-vertebral fracture risk  
5 reduction you see across drugs, because non-vertebral  
6 fractures are difficult to prevent with just  
7 antiresorptive therapy, because their etiologies are  
8 so complex.

9 DR. ROSEN: So that's correct. So I  
10 think -- and maybe you can help me, Steve. I don't  
11 want to get this into a personal conversation between  
12 you and I, but when we talk about weighing risk versus  
13 benefit and we have 20 percent non-vertebral fracture  
14 risk reduction where patient specific outcomes are  
15 involved, and then you have these rare events that are  
16 not quite statistically significant or may be barely  
17 statistically significant like neoplasm, how do you  
18 balance those two events? Because I think this is  
19 actually at the crux of the problem.

20 We have rare events that are occurring  
21 because you're studying lots of people and you have  
22 effect sizes that are similar to the other drugs.

1           DR. CUMMINGS: I can speak to the benefit  
2 side and, as you know, clinically, it's important to  
3 assess the risk of an individual patient, which can be  
4 done both with bone density and other considerations.  
5 And so this ends up being a clinical judgment about  
6 the risk of the patient that's sitting in front of you  
7 based on the age, their bone density and other things  
8 and the degree that their risk is increased, the  
9 benefits from non-vertebral fractures, as well as  
10 vertebral fractures, will be an important  
11 consideration in making the decision to treat and  
12 treat with this agent.

13           DR. EISENBERG: And again, the rates in  
14 terms of risk are very low, absolute rates, both for  
15 SAEs, are low. And the rates for malignancy, just to  
16 be clear, are not statistically significant for any of  
17 the events we've talked about today.

18           DR. ROSEN: No. Well I understand, it's  
19 just that they're rare events and you'll see them in  
20 the 300,000 follow up people as well.

21           DR. CARSON: Dr. Collins?

22           DR. COLLINS: Should this drug be approved,

1 it'll be available for use in pre-menopausal women and  
2 children as well, theoretically, off label of course.  
3 But what do we know about safety in pregnancy and or  
4 children from the animal studies, the non-human  
5 primate studies?

6 DR. EISENBERG: Well, we do know that -- as  
7 was highlighted by Dr. Lacey in the embryogenesis  
8 process, that the inhibition of RANK ligand has many  
9 effects. So it certainly would not be a drug we would  
10 want a woman who's pregnant to be exposed to.

11 In terms of reproductive effects, there  
12 aren't any specific known effects of inhibition of  
13 RANK ligand in terms of reproductive effects. In  
14 children, we have programs for pediatric  
15 investigation.

16 It turns out, for example, that giant cell  
17 tumors, which are an unusual tumor, are driven almost  
18 entirely through the RANK pathway and we have some  
19 evidence that inhibition of RANK ligand is very  
20 helpful for those patients. But one has to be careful  
21 because of the effects on developing bone, not to  
22 treat pediatric populations before the FCL plates have

1 fused. So those would be the general concerns, and we  
2 certainly would have labeling that it should not be  
3 used in a pregnant woman.

4 DR. COLLINS: So this does cross the  
5 placenta I guess then.

6 DR. EISENBERG: We don't have data that it  
7 does, but clearly, an abundance of caution would be  
8 appropriate.

9 DR. CARSON: And the final question, I'd  
10 like to bring up again. I'm concerned -- I want to  
11 bring up the weight data again that we began to talk  
12 about, that in Study 216, we see no change in  
13 fractures after three years, but a significant change  
14 in bone mineral density. And then that surrogate  
15 marker for fracture becomes our primary outcome in the  
16 other studies. And although we see a definite change,  
17 we also see changes.

18 Do we expect still, no fracture change? And  
19 so it seems that there is a little bit of  
20 disassociation between the actual bone mineral density  
21 change and the fracture risk. And when you consider  
22 that in light of the difference between the denosumab

1 and placebo groups, the bone mineral density changing  
2 in that group with different body weight, I think it's  
3 somewhat concerning.

4           You make the point that bone mineral density  
5 changes less in the placebo groups with higher weight,  
6 and I gather that's what your explanation of is the  
7 difference.

8           It still concerns me that should we be  
9 considering weight in our patient -- in our sub --  
10 when you do the subgroup analysis for weight, is that  
11 something we should be considering in which groups  
12 would benefit most by treatment?

13           DR. STEHMAN-BREEN: Just to clarify, the  
14 absolute changes in bone mineral density are the same  
15 across body weights. Let me highlight the consistency  
16 of effect that we've seen for new vertebral fracture  
17 year-by-year.

18           So this analysis was done looking at the  
19 incidence of vertebral fracture between zero and 12  
20 months, 12 and 24 months, and 24 and 36 months. And  
21 as you can see, there is great consistency of effect  
22 when you look at new vertebral fracture. You see

1 similar sustainability of effect when you look at non-  
2 vertebral fracture.

3           In the FDA presentation, they highlighted  
4 the hip bone mineral density during that third year,  
5 There was a very small number of fractures, but there  
6 were slightly more numbers of fractures in the placebo  
7 group, but it's important to highlight that the  
8 fracture rates in the placebo group were actually  
9 declining over time.

10           The fracture rates in the placebo group were  
11 sustained. This suggests that it's possible that in  
12 the denosumab group, this suggests that there may be a  
13 survivorship phenomenon in the placebo group that's  
14 resulting in fracture rates that over time declined.  
15 So you have a healthier group in the placebo group  
16 over time, perhaps due to some drop out, perhaps due  
17 to fractures. So again, the lack of difference you  
18 see in the third year is primarily driven by a decline  
19 in the fracture rates in the placebo group, rather  
20 than a lack of sustained effect in the denosumab  
21 group.

22           Now with all of that said, the treatment by



1 time interaction was not different. The Kaplan-Meier  
2 curves continue to show separation at three years. So  
3 the totality of this data together suggests that we do  
4 have a sustained effect with regard to fracture over  
5 the three year period of the study.

6 DR. CARSON: There's no change in that third  
7 year, but yet there's a significant decrease in BMD.

8 DR. STEHMAN-BREEN: So it's a relative --  
9 oh, there's no significant decrease in BMD during the  
10 third year; If we can pull up the bone mineral density  
11 slide.

12 You can see that bone mineral density  
13 continues to increase over the three years of the  
14 study. Now it's expected that most of the increases  
15 in bone mineral density will be seen in the first year  
16 of the study, due to mineralization. This is a  
17 phenomenon that's observed with any therapeutic for  
18 osteoporosis.

19 DR. CARSON: I misspoke, but what I'm saying  
20 is you see a difference in bone mineral density, but  
21 yet no difference in fracture rates.

22 DR. STEHMAN-BREEN: We do. We continue to

1    see -- if you can please put the vertebral fracture,  
2    year-by-year data up.

3               At the third year, we continue to see a  
4    significant -- 65 percent reduction in new vertebral  
5    fracture, which is very similar to the overall 68  
6    percent reduction that we see over the entire three-  
7    year period.

8               If you look again at non-vertebral  
9    fractures, we see a very similar phenomenon where  
10   every time period, zero to 12 months, 12 to 24, 24 to  
11   36, you see very similar levels of reduction. And if  
12   you can put the slide up, you can see that you see  
13   similar relative reductions in non-vertebral fracture  
14   risks favoring denosumab in each of those three time  
15   periods.

16              DR. CARSON: Could we see the hip as well?

17              DR. STEHMAN-BREEN: I believe we have a  
18   slide that has the incidence rates across all studies.

19              If you could put the slide up, across the  
20   PMO fracture study. So here you can see new vertebral  
21   fracture, non-vertebral, hip, major osteoporotic and  
22   clinical vertebral fracture.

1           DR. EISENBERG: And it's very clear what's  
2   happening. If you focus on hip fracture, these are  
3   the same data that were shown earlier by FDA, the rate  
4   in placebo is what's going down. And again, keep in  
5   mind the design of the study to protect placebo  
6   treated patients, because they got best standard of  
7   care, Vitamin D and calcium. You expect the higher  
8   risk patients will actually over time come out of the  
9   study, because they would have been more clinical  
10   concern. But the effect of denosumab in every study  
11   we've done, including the preclinical studies, all of  
12   the data does not change over time.

13           DR. CARSON: And again, I hate to harp on  
14   this, but again, you say the difference between the  
15   denosumab and placebo groups decreased with increasing  
16   body weight.

17           DR. STEHMAN-BREEN: Why don't I have Dr. San  
18   Martin, who is responsible for those analyses,  
19   elaborate on this further?

20           DR. SAN MARTIN: I'm sorry. Maybe I didn't  
21   answer the question well in the morning.

22           Can I have first the slide with that shows

1 in the X axis the weight and in the Y axis, the bone  
2 mineral density?

3 So you can see in the X axis different body  
4 weight and in the Y-axis change in bone mineral  
5 density. And obviously, there is no correlation  
6 between changes in bone mineral density and baseline  
7 body weight. Same is true for bodyweight PK or  
8 expression to denosumab.

9 So there is really no relationship between  
10 BMD changes and body weight. Now because the patient  
11 who has high body weight, tends to not lose bone  
12 mineral density that much than between denosumab and  
13 placebo may now be -- are the same when you see the  
14 patient with very low BMI and those with higher BMI,  
15 but that's not affected in this slide.

16 DR. CARSON: This is really not an answer to  
17 my question. I'm saying that in the 70 kilogram  
18 weight group, for example, you have a difference  
19 between your treatment and your placebo group than  
20 in -- so that says to me that women who weigh a little  
21 bit more are not going to benefit by this drug as much  
22 as women in a --

1           DR. SAN MARTIN: That's a good point. Let  
2 me show you this slide please.

3           So the third bullet point represents the  
4 changes in bone mineral density for patients with  
5 different body weight between denosumab and placebo.  
6 And as you see, the difference is smaller in this  
7 patient with higher weight at baseline. And the  
8 reason of that in part is because this is expressed in  
9 percent change, and the baseline BMD in those patients  
10 with heavy weight are higher.

11          So the absolute gains in bone mineral  
12 density is essentially the same, despite the baseline  
13 weight. I don't have a slide that specifically  
14 addresses your question, but we did perform that  
15 analysis, and clearly -- oh here, this is the  
16 fracture.

17          So I already showed you the fracture  
18 reduction, which is consistent across all body weight.  
19 But again, the bone mineral density difference is  
20 essentially due to the baseline difference in bone  
21 mineral density across different patients with  
22 different baseline weight.

1 DR. STEHMAN-BREEN: Just to reiterate,  
2 regardless of weight, denosumab results in a similar  
3 absolute increase in bone mineral density.

4 DR. SAN MARTIN: That's right.

5 DR. CARSON: Dr. Buzdar?

6 DR. BUZDAR: Yeah, one question which I  
7 wanted to ask was that if you showed the data in year  
8 one, two and three, and according to your initial  
9 reports that you have observations up to six years,  
10 the question is that after that, what happens to the  
11 difference in fracture rate? Do they start to become  
12 closer to each other? Do you have any slide to show  
13 that?

14 DR. EISENBERG: Well the only  
15 time -- because, again, these are -- well best  
16 standards of care, other than a biphosphonate or  
17 raloxifene treatment, it's not ethical to continue  
18 patients on long-term comparisons to no treatment,  
19 because these are patients with osteoporosis.

20 So the long-term data, after three years,  
21 everybody that we're following, the 4,550 patients  
22 that I highlighted in the presentation, all of those

1 patients will receive denosumab, and we continue to  
2 monitor those rates, but we can't compare them to  
3 placebo.

4 Is that what you're interested in or am I  
5 not getting it right?

6 DR. BUZDAR: No, that's exactly the point.  
7 Even let's say that they get crossed over from placebo  
8 to now your active drug. The question is, is there  
9 any difference? Do those differences disappear? I  
10 think it will be still important, because some of the  
11 oncology trials -- timing of initiation of therapy  
12 also makes significant difference.

13 Dr. STEHMAN-BREEN: So I just want to  
14 clarify, the data that we have out to six years is  
15 from our Phase 2 study, where we have a long-term  
16 follow up period, that's not a very large study, as  
17 you can imagine, now that we're out to six years. And  
18 so it's really not a study -- in addition it's not  
19 placebo controlled. And so it would be really for  
20 multiple reasons, and so, it would be, really, for  
21 multiple reasons, not possible to look at fracture  
22 rates in that study.

1                   Now the other study that was being  
2 highlighted is the long-term extension study from our  
3 big fracture study. And again, the extension period  
4 has only been going on for a year so. When that data  
5 becomes available, Dr. Cummings as head of our  
6 Steering Committee and now our Publication Committee,  
7 is working on analyses that will allow him to do  
8 analyses that he calls virtual twin models, that will  
9 help us understand the fracture rates over time.

10                  DR. CARSON: Okay. Thank you very much.

11                  It's very clear that you're well familiar  
12 and the whole team knows the data. Let's now address  
13 the questions that are asked to us.

14                  For this session, we will have time to  
15 discuss and we'll be using the new electronic voting  
16 system for this meeting.

17                  Each of you panel members have three voting  
18 buttons on your microphone: yes, no, and abstain.  
19 Once we begin the vote, please press the button that  
20 corresponds to your vote. The final vote will then be  
21 displayed on the screen. I will read the vote from  
22 the screen into the record. Next, we will go around



1 the table and each individual who voted, will state  
2 their name and vote into the record as well as the  
3 reason why they voted as they did.

4 So let's begin with question 1A.

5 Is there a population of post-menopausal  
6 women with osteoporosis in which the benefit of  
7 treatment with denosumab is likely to outweigh the  
8 risks? And if you would vote now.

9 DR. PAZDUR: There's no discussion of this  
10 question? People don't want to discuss this before  
11 they vote. Going, going once, twice.

12 DR. CARSON: I think we would like to  
13 discuss -- discuss before we vote is okay. Okay.

14 DR. BUZDAR: I think the way the question is  
15 put, maybe we need to discuss. It's a very ambiguous  
16 question.

17 DR. CARSON: Why don't you begin?

18 DR. BUZDAR: Yeah, I think the thing is that  
19 question, if I read it, is there a subgroup in which  
20 the risk is greater than the benefit. That's what  
21 you're trying to ask?

22 DR. CARSON: Is there a sub -- it says -- is

1    there a subgroup that, right, would most likely  
2    benefit more than the risks that you've heard today?  
3    Any particular subgroup in the group of osteoporotic  
4    post-menopausal women?

5               DR. ROSEN:   Okay.  I think that you're  
6    referring to treatment, correct?  Not prevention.  
7    This is directly related to treatment.

8               DR. CARSON:  Right.

9               DR. ROSEN:  Right.

10              DR. CARSON:  This is post-menopausal women  
11    with osteoporosis, and would treating their  
12    osteoporosis receive more benefit than risk?

13              DR. NELSON:  The way I would read the  
14    question is, it doesn't necessarily have to be all  
15    post-menopausal women would benefit.

16              Is there a group of women?

17              DR. CARSON:  It's post-menopausal women who  
18    already have osteoporosis, are there groups already in  
19    that group that would benefit.

20              Dr. Emerson?

21              DR. EMERSON:  Well I guess I'd come down on  
22    the decision.  First of all, I mean I think separating

1 out groups, subgroups of the clinical trial, would be  
2 fraught with peril, personally. But in the large  
3 clinical trial with 8,000 women, they had a benefit,  
4 but the number needed to treat is all important to me.  
5 And, basically, numbers agree with much of the  
6 sponsors, but roughly to prevent any fracture, you'd  
7 need to treat 16.

8           To treat hip or vertebral fractures, it's  
9 18. But by the time you get up to hip, it's 200. And  
10 the question there then, a lot revolves around how  
11 important the vertebral fracture is for quality of  
12 life. And my inclination, not knowing anything else  
13 but testimony on this, is that that's pretty high, as  
14 compared to going with the non-significant results,  
15 interpreting just as if they were known, the roughly 1  
16 to 1 and a half percent difference in serious adverse  
17 events of every kind, that likely the decrease in  
18 quality of life from the fractures in this population,  
19 the sort of population they were tested was worse from  
20 the fractures than it is from the unknown risks that  
21 haven't totally been quantified.

22           So I guess I'm sort of down on the side of

1     saying, for the treatment as defined in that trial,  
2     it's looking like that group would benefit.

3             DR. CARSON:   And that group -- the whole  
4     group.

5             DR. EMERSON:   Is that the inclusion criteria  
6     in that whole clinical trial.

7             DR. CARSON:   Dr. Richardson?

8             DR. RICHARDSON:  Well, I think there's a lot  
9     of difference among these vertebral fractures though.  
10    I mean if you're talking about somebody who really  
11    crunches down their vertebra, obviously that's major  
12    event fraught with pain, a lot of morbidity.  But we  
13    see a lot of guys who -- when you look at the lateral  
14    views on their chest x-rays -- they've got a little  
15    bit of loss of height anteriorly on one or two  
16    vertebra, they're totally unaware of it.  And are you  
17    counting those in your vertebral fractures?

18            DR. EMERSON:  There's no question that they  
19    were using the subclinical increase in vertebral  
20    fracture as a new vertebral fracture.  So if they had  
21    that -- some level of compression they saw, if it had  
22    increased by a certain amount in some vertebra, it was

1 counted as a new fracture. And I'm not certain what  
2 the significance is, other than this is a group of  
3 women who already have severe osteoporosis at a  
4 level -- 24 percent have had previous fractures.

5 DR. CARSON: Dr. Rosen?

6 DR. ROSEN: Yeah, I would favor  
7 Dr. Emerson's position. I actually think for a bone  
8 active drug, this is as good as it gets for non-  
9 vertebral fractures. Even forgetting about vertebral  
10 fractures and whether they're silent or not, but  
11 remember silent vertebral fractures have an increased  
12 risk of mortality and morbidity anyways. So with  
13 numbers needed to treat less than 20, that's pretty  
14 impressive for people who suffer from osteoporosis.

15 And in that group, in that cohort, that's a  
16 highly effective group, multiple fractures in many  
17 cases, and very low bone density. So I certainly  
18 favor yes on this particular issue.

19 DR. CARSON: And would you clarify what  
20 subgroup then of post-menopausal women with  
21 osteoporosis you would favor yes to.

22 DR. ROSEN: So I mean I think you have to

1 look at the cohort. And the cohort is T-score is less  
2 than minus 2.5, the average age is over 70, and about  
3 a third of them have fractures if I remember  
4 correctly. But that's a high risk subgroup. That is  
5 the group that they designate to look at fractures,  
6 because those are the ones that are most likely to  
7 fracture.

8               So I think it would be very difficult to  
9 parcel out individual subgroups from that. I think  
10 for a treatment of post-menopausal established  
11 osteoporosis, it fits.

12              DR. CARSON: So then you're really saying  
13 the answer should be no, right? That it's the whole  
14 group --

15              DR. ROSEN: Well I think Dr. Nelson  
16 summarized it correctly. The way the question is  
17 phrased, in a population of post-menopausal women with  
18 osteoporosis, is the benefit of treatment likely to  
19 outweigh the risk? And I would say the answer is yes  
20 to that.

21              DR. CARSON: Dr. Margolis?

22              DR. MARGOLIS: Yeah, I would agree with both

1 Dr. Emerson and Dr. Rosen. I would agree that based  
2 on the data from the clinical trial for the population  
3 that was studied in the clinical trial, it appears the  
4 drug is effective. I think what is very dangerous is  
5 we're going to go into that clinical trial and all of  
6 a sudden decide there's one subgroup that's better  
7 than another. The study wasn't designed to do that.  
8 As an epidemiologist, I would strongly discourage  
9 people from doing that.

10 If people are concerned about their risk,  
11 that really then goes to the importance of question  
12 number 6 in terms of how things are going to be viewed  
13 in the future in terms of post-marketing studies and  
14 risk discussions with physicians and patients.

15 DR. CARSON: Dr. Nelson?

16 DR. NELSON: The other thing I read into  
17 question one is, is this an effective drug and should  
18 it be out there for clinicians to be able to make a  
19 decision on individual patient -- yes, this is a  
20 severe enough case that we can use this agent. That's  
21 what I think should be used to determine the answer to  
22 question 1, so I would say yes.

1                   DR. CARSON: Any other discussion? Okay,  
2 I'd like FDA staff to correct this if I'm wrong.  
3 We're going to ask this question, assuming that the  
4 population that we're voting for is the study  
5 population rather than subgroups within post-  
6 menopausal women. So a yes would mean that the study  
7 population or population of post-menopausal women  
8 would benefit from treatment more than they would have  
9 a risk of treatment.

10                   So is there a population of post-menopausal  
11 women with osteoporosis in which the benefit of  
12 treatment with denosumab is likely to outweigh the  
13 risks?

14                   So please -- we can't vote. Okay, now we  
15 can.

16                   Now will the lights go off when our vote is  
17 registered? Okay, let's try again.

18                   Okay. There are 15 votes. Is that correct?

19                   Are there 15 voting members of the  
20 committee? Then the result is that unanimous, all  
21 committee members voted yes.

22                   So let's begin with Dr. Gut. And will you



1 read your vote into the record and state why you  
2 voted?

3 Oh, you're not voting. Oh, okay.

4 MS. SOLONCHE: Martha Solonche, and I voted  
5 yes. There is a population of post-menopausal women  
6 with osteoporosis who will have benefit from this drug  
7 that will outweigh the risks.

8 DR. CARSON: Dr. Gulley?

9 DR. GULLEY: Yes, clearly I think that -- I  
10 voted yes, clearly that Trial 216 managed primary  
11 endpoint, and this was a clinically significant  
12 finding, too, besides being statistically significant.

13 DR. RICHARDSON: Ron Richardson. I voted  
14 yes with some concerns however. I'm not sure why --  
15 that we've identified that subgroup, and I think I'm  
16 concerned about the fact that we are exposing a lot of  
17 healthy people to risks.

18 DR. MORTIMER: Joan Mortimer. I voted yes  
19 because the study met its primary endpoint. There was  
20 a decrease in vertebral fractures.

21 DR. BUZDAR: Yeah, Buzdar. I voted yes. I  
22 think overall there was significant reduction in all

1 fractures. Still I think the question about the  
2 safety, I still have reservation, but I think overall  
3 from the efficacy point of view, there was marked  
4 reduction and I support that.

5 DR. MARGOLIS: David Margolis. I voted yes,  
6 based on the results that were present from study I  
7 guess 216. However, I think the risk evaluation  
8 mitigation strategies that we'll discuss later will be  
9 very important.

10 DR. NELSON: I voted yes because the  
11 evidence shows that this is effective in reducing  
12 fractures in this population. And the agent, in my  
13 opinion, should be available for clinicians, then  
14 weigh the risks that have been outlined here to decide  
15 whether to use it in an individual patient.

16 MR. GOOZNER: I voted yes, a little bit  
17 reluctantly. To repeat what people said, it is  
18 overwhelming that this drug works for what it was  
19 designed to do, but I think because of the unknown  
20 quantity of the risks -- and we'll discuss more about  
21 this later -- I definitely think that it ought to be  
22 used almost like a second line therapy for when people

1 find they're intolerant or have not been effective  
2 with the other drugs that are already out there.

3 DR. JOHNSON: Yes, Julia Johnson. I also  
4 voted yes. I will mirror what others have said in  
5 that I have significant concerns about potential long-  
6 term effects of this medication, whether it's over  
7 suppressive on bone turnover and whether it causes  
8 immunosuppression, which can lead to infection or  
9 cancer.

10 I think that we need to look at this very  
11 closely, and I think if this is a unique medication  
12 and therefore beneficial to women who do not tolerate  
13 other medications that prevent fractures. But I do  
14 think we need to talk about that extensively when we  
15 talk about question 6.

16 DR. CARSON: Carson. I voted yes, because  
17 it decreases fracture risk in this population.

18 DR. EMERSON: Scott Emerson and I voted yes,  
19 because I felt that this is a patient population that  
20 was seeking treatment for their disease, and that  
21 while there are uncertainties about the long-term  
22 safety and the very rare conditions, that I felt that

1 the incidence of the complications of this disease in  
2 this patient population warranted a treatment.

3 DR. BENNETT: John Bennett. I voted yes,  
4 because of the very well done Study 216. I  
5 congratulate the company on a very well done,  
6 carefully analyzed trial.

7 I'd want to comment something about so-  
8 called asymptomatic vertebral fractures. I think  
9 there are patients in the intensive care unit who are  
10 ventilated who are so kyphotic that they're very  
11 difficult to ventilate. I think they're patients who  
12 have back pain that's probably due to these fractures  
13 and it's hard to know whether or not they are. But I  
14 think we've heard from some of our commentaries from  
15 the public about the pain that goes along with this.  
16 So knowing exactly how many are due to these  
17 fractures, its difficult to say, but I think that's  
18 part of the morbidity that we're trying to prevent  
19 with this drug.

20 DR. UZEL: Gulbu Uzel. I voted yes, because  
21 I believe, as supported by the evidence presented here  
22 today, that this drug is effective in preventing

1 osteoporosis in the population targeted.

2 DR. ROSEN: I'm Cliff Rosen. I voted yes  
3 for the reasons I stated previously and everybody else  
4 has stated since.

5 DR. COLLINS: Mike Collins, I voted yes.  
6 Like Cliff, for the same reasons. I would add,  
7 though, or echo anyway, the concern for careful long-  
8 term follow up and in consideration of other dosing  
9 regimens that might get the same benefit.

10 DR. CARSON: Okay. We have some discussion  
11 but no vote for question 1B. And that is, since we  
12 voted yes, would this population be all women with  
13 post-menopausal osteoporosis or limited to a subgroup  
14 at a high risk for fracture defined as a history of  
15 osteoporotic fracture, multiple risk factors for  
16 fracture, or women who have failed to receive benefit  
17 from or are intolerant to other osteoporosis  
18 therapies?

19 Dr. Rosen?

20 DR. ROSEN: Yeah, I could start. I mean I  
21 think that it probably is not first line therapy. I  
22 think, obviously, there are a lot of things that go

1   into -- cost is one thing and safety obviously is a  
2   second thing.  And I do believe that there are, as we  
3   heard today, some people who cannot tolerate  
4   biphosphonates, who would be better off with a  
5   relatively simple regimen.

6               So I think there probably should be  
7   defined -- something in there to guide practitioners  
8   in terms of using this drug as first line or a second  
9   line and this will be guided by several factors; I  
10  think safety being one of them that all of us are  
11  concerned about.

12              DR. CARSON:  Mr. Goozner?

13              MR. GOOZNER:  Yes, I think the one thing  
14  that needs to be said here is that this is a first in  
15  class drug and it's a monoclonal antibody.  And  
16  historically, it was very wise to rollout first in  
17  class drugs like this, especially where there's other  
18  treatments available in a rather slow fashion so that  
19  risk can emerge over time.  And I think that I would  
20  change this number 2 as written to say not women who  
21  have failed "or" intolerant of other, but make that  
22  "or" into an "and".

1           I think this should be a drug that is used  
2   in people who are at high risk, who sort of look like  
3   the people who are in this trial and who clearly can't  
4   use the other things that are out there or who have  
5   failed on them. And that way, over a few years, we'll  
6   get a much greater experience of what the real risk  
7   profile is of the people on this drug.

8           DR. CARSON: Let me just comment that if we  
9   change it to an "and", we would be excluding all those  
10  who are intolerant of it, because they would not have  
11  been able to take it long enough to fail. So it has  
12  to be "or".

13           Dr. Margolis?

14           DR. MARGOLIS: Yeah, I would be very careful  
15  again about using this drug in a population of  
16  predicting how it's going to work other than the  
17  population that was tested. So unless the inclusion  
18  criteria was that somebody had failed biphosphonate  
19  therapy, it makes it very difficult to know just how  
20  successful would it be in that population. So  
21  practically, it may end up being a second line drug  
22  because of concerns about risks, but how we could

1 possibly know how well it would work in that  
2 population is well beyond the data presented today.

3 DR. COLLINS: But you know, I think if --  
4 I'm sorry. If you're the clinician sitting there with  
5 the patient and they failed all the other options, you  
6 have -- it's as intolerant to other osteoporosis  
7 therapy. So you have to decide and you have to make a  
8 choice. So when you're there with the patient in  
9 front of you, you don't have everything you need all  
10 the time.

11 DR. CARSON: Dr. Johnson?

12 DR. JOHNSON: Yes, and I would agree with  
13 whatever everyone else has said and encourage the  
14 company to not encourage this to be a first line  
15 therapy.

16 DR. CARSON: Dr. Buzdar?

17 DR. BUZDAR: I think the thing is that if we  
18 look at number 1, which says all women with post-  
19 menopausal osteoporosis, that is not the study  
20 population which was included. So I think that will  
21 be giving a label indication beyond the study  
22 population. So it will be, I think -- I don't know



1    why we're even discussing about it, because there is  
2    no data in that subset of patient population.

3               DR. CARSON:  Any other comments?

4               So I feel that the committee has come to a  
5    consensus that this drug -- first, the committee has  
6    voted that there is benefit to giving denosumab in a  
7    population of post-menopausal women with osteoporosis  
8    and these benefits outweigh the risk.  I feel that the  
9    committee's consensus is that the drug should be  
10   limited to a high risk subgroup, high risk for  
11   fracture, with a history as tested by the data  
12   presented, with a history of osteoporotic fracture or  
13   with high risk for fracture as well as in those  
14   patients who have either failed or are intolerant of  
15   other therapeutic measures.

16              Dr. Rosen?

17              DR. ROSEN:  Yeah, I just want to clarify  
18   that this group of individuals -- to design this study  
19   to show fracture efficacy, these are relatively high  
20   risk individuals.  They're over 65.  They have  
21   T-scores less than minus 2.5.  More than a third of  
22   them have fractures, prevalent fractures.  So I mean I

1 think we have to be careful about subgroup because I  
2 think it's very important to remember these are true  
3 osteoporotic women.

4           They're at high risk, their FRAX risk  
5 indicators are 7 percent for hip fracture, which is  
6 well above the 3 percent threshold. So just a  
7 reminder that this is a relatively homogeneous group  
8 of women that we deal with that have post-menopausal  
9 osteoporosis established.

10           DR. CARSON: Let's move on to question 2.

11           DR. RICHARDSON: May I ask a question first?

12           DR. CARSON: Sure.

13           DR. RICHARDSON: Based on what you're saying  
14 Dr. Rosen, are we going to specify some sort of  
15 criterion, I mean FRAX criteria for that risk  
16 stratification for this group?

17           DR. ROSEN: No, I don't think we should.  
18 I'm just commenting on what the demographics of this  
19 population that they studied are, but I would be very  
20 loathe to specify a FRAX indicator. That data set  
21 continually changes, and I'd be very worried about  
22 using a FRAX threshold.

1 DR. RICHARDSON: But what does that mean for  
2 the clinician in practice? He can look at somebody,  
3 give them the eyeball test, and say I think you're at  
4 risk and treat?

5 DR. ROSEN: Well, I mean, I think we  
6 tend -- I mean, as Dr. Siris said, we now have lots of  
7 indicators for establishing risk. And if you have a  
8 high risk individual, this becomes one of the  
9 potential drugs that might be utilized in that  
10 situation. And I think that's all you can say. And,  
11 of course, we have to balance risk with benefit. But  
12 I think in terms of a practitioner looking at a  
13 patient, there are now several options that they can  
14 use.

15 This may not be a viable option, because  
16 it's so expensive as a first line therapy, for  
17 example. But it puts into the armamentarium and I  
18 think that's all we say, that this is one of the drugs  
19 that has about the same NNT as any of the  
20 biphosphonates and is effective.

21 DR. RICHARDSON: Well if you're a guy in  
22 practice and you've got a patient who comes in and you

1 can administer this drug parenterally in your office  
2 versus handing them the script for Fosamax, what's  
3 going to happen?

4 DR. ROSEN: Well, I think you have to take  
5 the whole patient into consideration, what kind of  
6 insurance do they have? Do they cover it? What's  
7 their compliance history? I mean, I think -- you've  
8 heard -- and this is a huge problem in the  
9 osteoporosis field -- compliance is 25 to 40 percent  
10 after one year. So it's really essential that we try  
11 to get at therapies that people can comply with. It  
12 may not be the first line of therapy and it may be  
13 that people are failing because they're not taking the  
14 drug, but there it is. You would have another option.

15 DR. CARSON: Moving on to question number 2.  
16 Is there a population of post-menopausal women with  
17 low bone mineral density who do not meet the criteria  
18 for treatment of osteoporosis, in which the benefit of  
19 prevention of osteoporosis with denosumab is likely to  
20 outweigh the risks?

21 So basically the same question, but for  
22 prevention of osteoporosis in women who have low bone

1 mineral density. So they don't have osteoporosis,  
2 they have osteopenia, and is there an indication for  
3 prevention of osteoporosis?

4 Dr. Collins?

5 DR. COLLINS: I think the answer is yes, but  
6 we don't know who they are.

7 DR. CARSON: Dr. Emerson?

8 DR. EMERSON: Well I mean my answer is going  
9 to be no, but I have to change this question very  
10 slightly in the sense of there's evidence that it's  
11 likely. And this is the problem, is that I just don't  
12 think that there's evidence in this group that it was  
13 tested in 300 women, in this group were being  
14 compared.

15 So only half that number on the treatment  
16 arm that -- I raised my objections to the FRAX being  
17 the 10 year time frame. I can see that that's very  
18 important for the individual women to be able to look  
19 at that prognosis, but it's not clear to me that a  
20 prevention strategy is in order yet, or that a  
21 treatment strategy is in order yet. And here's where  
22 the uncertainty in some of the more serious adverse

1 events just means we'd -- I'd like to have more data  
2 before I'd vote yes on this.

3 DR. CARSON: Dr. Rosen?

4 DR. ROSEN: Yes. So I would just like to  
5 reinforce that the sponsor actually did the right  
6 study because your only power -- you only need 300  
7 subjects to show a very significant effect on bone  
8 density. The problem is does the risk justify the  
9 benefit with a large population where generally  
10 numbers needed to treat are in the 2,000 range to  
11 prevent fracture? Not to change bone density, which  
12 is not a patient specific outcome, but to change  
13 quality of life.

14 That's where the issue comes in, and here  
15 the uncertainty around treating large numbers of  
16 people with osteopenia -- and you saw the numbers are  
17 absolutely huge -- would be an indication. And I'm  
18 quite concerned that we still don't have enough safety  
19 data at three years out to be certain that we can  
20 advocate for a prevention study at this stage.

21 DR. EMERSON: And so just to clarify this  
22 whole point to saying that in this group, in the

1 treatment group, we showed that we could increase bone  
2 mineral density and we could decrease fractures. And  
3 there's one level to say, is that proof that the bone  
4 mineral density is a surrogate. But let's look at  
5 lowering blood pressure. If you take hypertensives  
6 and lower their blood pressure, you also improve their  
7 survival. But if you take normotensives who are at  
8 high risk for eventually developing hypertension and  
9 lower their blood pressure, it doesn't obtain. And we  
10 just don't have that information. And there's  
11 certainly just a suggestion that this isn't distilled  
12 water we're giving them, that there might be more of a  
13 risk involved.

14 DR. CARSON: I personally think that this is  
15 where the safety really comes into play, because what  
16 we're really talking about is a bone mineral density  
17 number. I mean, it was decided, okay, two standard  
18 deviations below or a T-score of minus 2 is osteopenia  
19 and minus 2.5, it's osteoporosis. And what we're  
20 talking about is can we prevent that.

21 Well this drug, certainly we've seen that it  
22 does prevent bone mineral density loss. So if we're

1 talking about those numbers, the answer has to be yes.  
2 But then what does safety -- because that's a numbers  
3 games and that's what I kind of worry about all of  
4 these surrogate markers that we use, and especially  
5 when we don't exactly know differences between  
6 subgroups of numbers.

7 But when you look at the risk of osteopenia  
8 as a number for fracture and developing further, it  
9 does progress to osteoporosis and fracture. So I  
10 think there is some benefit. But then that's when  
11 safety becomes important, and I think that we have to  
12 be very conscious of what we're doing long-term with  
13 safety.

14 Having said that, I think it's also  
15 important that when this drug is stopped, bone mineral  
16 density does plummet. And so that means we're talking  
17 about if we believe that this group is important to  
18 treat because of this number, we're talking about  
19 long-term therapy, and we better be convinced of its  
20 safety.

21 DR. NELSON: My opinion would be the answer  
22 to this is no, because there is this biologic



1   plausibility of immunosuppression increasing risk of  
2   infections and increasing risk of cancers. And when  
3   we're dealing with a preventative approach, we really  
4   need to make sure that this isn't going to cause any  
5   harm or cause minimal harm. So my answer would be no  
6   on this.

7                   DR. CARSON: Dr. Mortimer?

8                   DR. MORTIMER: But I think we have to  
9   appreciate that this population is at higher risk. I  
10   mean, Dr. Siris went through the NORA study that  
11   showed us that people in this group that would be  
12   included in the study are in fact at increased risk.

13                  But I go back to Dr. Rosen. I mean, I just  
14   don't think we know who those patients are. And if  
15   the primary endpoint for approval on an osteoporotic  
16   drug is decreased fracture rate, I think in prevention  
17   it should also be decreased fracture rate. So we  
18   don't know that.

19                  DR. CARSON: Any other committee discussion  
20   before we vote?

21                  Okay, we'll try to vote. Not yet. Now.

22                  Okay everybody, would you please vote again?

1           Somebody isn't registering. Yes, no, or  
2   abstain. If you don't want to vote, just press  
3   abstain. Vote again.

4           Okay, the voting results are there were  
5   three members who voted yes and 12 that voted no. So  
6   could we go around the room, and let's start with  
7   Dr. Collins this time.

8           DR. COLLINS: Yeah, I voted no, and the  
9   reason being that I just don't think we know what the  
10   population of patients is that will benefit. And  
11   until we know and until we know the long-term safety,  
12   I think I have to vote no.

13          DR. ROSEN: I voted no, because I'm also  
14   worried about safety, I just --

15          DR. CARSON: Would you say your name please?

16          DR. ROSEN: Oh, I'm sorry. Cliff Rosen. I  
17   voted no. So I just calculated the FRAX data set for  
18   the mean value in the prevention trial that they did,  
19   32, and the major risk of hip fracture is only 0.9,  
20   and the major osteoporotic fracture is 9 percent over  
21   10 years.

22          So if you take that into consideration,

1 we're talking about a relatively low risk group of  
2 individuals that do have osteopenia, and I think we  
3 don't have enough information yet about long-term  
4 safety. I'm still concerned about bone suppression in  
5 this group, so I think that's why I voted no.

6 DR. UZEL: Gulbu Uzel. I voted no for the  
7 same reasons. I don't want to repeat it.

8 DR. BENNETT: Bennett. I voted yes. I  
9 guess I'm less risk adverse. I don't see a strong  
10 signal here for concern, and I believe that post-  
11 marketing surveillance the company's projected is  
12 adequate to look at this. So we won't know until we  
13 try it, and I think we should try it.

14 DR. CARSON: Dr. Emerson?

15 DR. EMERSON: Scott Emerson and I voted no,  
16 because of the issues that I discussed earlier.  
17 Basically, that I think there's a lot of uncertainty  
18 in a low risk population, that the number needed to  
19 treat is sort of too high even in the most optimistic  
20 settings.

21 DR. CARSON: Carson, and I voted yes,  
22 because I was convinced by the data that this drug

1 does prevent loss of bone mineral density and that I'm  
2 confident that post-marketing surveys and studies will  
3 allow us to assess the long-term safety, which I agree  
4 is not quite there yet.

5 DR. JOHNSON: Julia Johnson. I voted no for  
6 the reasons that have already been stated.

7 MR. GOOZNER: Merrill Goozner. I voted no  
8 for the number needed to treat the unknown risks.

9 DR. NELSON: Larry Nelson. I voted no  
10 because of the reasons discussed and I think it'd be  
11 important to get more data on the more severe cases  
12 before we start using this for prevention.

13 DR. MARGOLIS: David Margolis. I voted no.  
14 I do believe that it diminishes bone mineral loss, but  
15 I have concern about the long-term safety, and as more  
16 long-term safety data is available, would certainly  
17 reconsider the vote.

18 DR. BUZDAR: Yes, Buzdar. I voted no. The  
19 reason being that here we expose a lot of patients,  
20 and still the safety data is, I would say,  
21 preliminary, and we need more safety data before we  
22 start to use this as a preventative agent.

1 DR. MORTIMER: Joan Mortimer. No, and for  
2 all the aforementioned reasons.

3 DR. RICHARDSON: Ron Richardson. I voted no  
4 for the same reason Joan did.

5 DR. GULLEY: James Gulley. I voted yes,  
6 because I thought that the trial met its primary  
7 endpoint and I thought that the pharmacovigilance  
8 plans that were laid out were good. I thought there  
9 may be a signal of some safety importance, but that  
10 signal may also be explained just by chance.

11 MS. SOLONCHE: Martha Solonche. I voted no  
12 due to safety concerns.

13 DR. CARSON: Okay. The committee voted no  
14 to this question that there is not a population of  
15 post-menopausal women with low bone density who meet  
16 the criteria for prevention of osteoporosis with  
17 denosumab that is likely to outweigh the risk. And it  
18 seems the consensus of the committee feels that this  
19 treatment, although it may be effective, is related to  
20 unknown risks, which may not make the benefit of  
21 prevention worthwhile.

22 And Dr. Rosen?

1                   DR. ROSEN: I'd just like to amplify on what  
2 Dr. Collins said, and that is that we don't know who  
3 these people are with osteopenia that are going to go  
4 on to fracture. We're not even sure we know who those  
5 people are who are going to lose bone mass  
6 prospectively. And so that represents a dilemma. And  
7 if we knew and could identify people who are rapid  
8 losers and also more susceptible to fracture -- but  
9 that's been the dilemma in this field for awhile, is  
10 trying to identify people with T-scores of minus 1.5  
11 or minus 1.6 who may go on to lose significant bone  
12 and fracture in the next five years. And we need more  
13 information on trying to identify that subgroup.

14                   Currently, I don't think the markers really  
15 give us that kind of insight. So there may be a  
16 subgroup population. I'm just not sure we can  
17 identify it at this stage.

18                   DR. CARSON: Okay, let's move on to  
19 question 3. Is a favorable risk benefit ratio  
20 demonstrated for denosumab for the treatment of bone  
21 loss associated with hormone ablation therapy in women  
22 with breast cancer receiving aromatase inhibitors?

1 Dr. Buzdar?

2 DR. BUZDAR: I think the thing over here, I  
3 have significant concern for two reasons. One is that  
4 there is a trend towards even higher incidence of  
5 breast cancer. Second, patients who are getting  
6 aromatase inhibitor therapy and were treated, there is  
7 slightly increased risk of the recurrence, which was  
8 not the endpoint, but there was at least a hint of  
9 that.

10 So here other bone strengthening drugs like  
11 biphosphonates, when they have been very evaluated in  
12 these subset of patients, there is even suggestive  
13 evidence of all sites recurrences are fewer. Over  
14 here, actually it is somewhat other way around.

15 So I have serious reservation in this subset  
16 of patients until we see more data. And the drug  
17 company has to provide the data where recurrence has  
18 to be an endpoint where they need to look at it.

19 You cannot just ignore that a reoccurrence  
20 is not an endpoint, which we are interested, because  
21 if the drug is having an adverse event and there are  
22 more recurrences, there are other therapies which may

1 be having otherwise lower risk of recurrence. This is  
2 not only in the bone but in the other sites.

3 DR. CARSON: Dr. Johnson?

4 DR. JOHNSON: Yeah, my concern with this  
5 question is that they really, at least in my mind,  
6 didn't look at treatment. They had a relatively small  
7 population base. They had relatively normal T-scores.  
8 And so I'm not sure that they've really looked at  
9 prevention effectively for this treatment. It was  
10 really more of a prevention study just looking at bone  
11 density. So I'm not sure they really address the  
12 issue of treatment.

13 DR. CARSON: Dr. Mortimer?

14 DR. MORTIMER: I'm going to sort of echo  
15 what Dr. Buzdar said, but to the data using  
16 biphosphonates in women who are on aromatase  
17 inhibitors did show an increase in bone mineral  
18 density in both hip and spine. However, that didn't  
19 not translate to a decrease in hip fractures, because  
20 then these patients stopped the drug. And what's kept  
21 the biphosphonate in breast cancer on endocrine  
22 therapy alive is the decreased risk of breast cancer



1 incidence. So I don't think changing bone density in  
2 this population is really that important an endpoint.

3 DR. CARSON: Dr. Emerson?

4 DR. EMERSON: And I would just concur and  
5 just add in that the standard that when you're trying  
6 to treat, basically what is a sign or symptom arising  
7 from cancer treatments, and not take into account the  
8 effect on the cancer therapy, I think that's always a  
9 bad thing to do. And this is just a great uncertainty  
10 in my mind, and I just think that that has to be  
11 verified that that's not a problem here.

12 The other point I'll say is that if I were  
13 going to extrapolate from one population or  
14 another -- because if we have no data on the fractures  
15 in this population, we have it either in the post-  
16 menopausal osteoporosis or we have it in the prostate  
17 cancer. And my tendency would probably be to  
18 extrapolate more from the prostate cancer in terms of  
19 the timing of the treatment and the external thing,  
20 and that basically there's not that much evidence in  
21 the prostate cancer; again, based on a number needed  
22 to treat that we're doing as much. And so I'm

1 extrapolating wildly there, but I just don't see the  
2 evidence. So it's not demonstrated.

3 DR. CARSON: Dr. Rosen?

4 DR. ROSEN: I just have a question, because  
5 I'm still a little confused. In the breast -- maybe  
6 Dr. Mortimer can help us on this.

7 So are you saying that biphosphonated  
8 treated women on aromatase inhibitors have a reduced  
9 risk of recurrent breast cancer? Is that true for  
10 oral biphosphonates?

11 DR. MORTIMER: That's true for IV  
12 biphosphonates.

13 DR. ROSEN: IV biphosphonates only.

14 DR. MORTIMER: And it's true with a decrease  
15 in cancer specific events, and that's also -- yes,  
16 there are a variety of instances where the  
17 biphosphonates actually look to have anti-cancer  
18 effects but --

19 DR. ROSEN: Right. But the only one that's  
20 been shown has been zoledronic acid.

21 Is that correct?

22 DR. MORTIMER: That's correct.

1 DR. CARSON: Mr. Goozner?

2 MR. GOOZNER: Yeah, actually I wanted to  
3 chime in on this point, because it was made -- the  
4 presentation was made to us several times that there  
5 was no drug, FDA approved drug, for people with  
6 cancer. This actually goes to the prostate cancer  
7 thing. And yet, when I went to the medical literature  
8 after what had been submitted to us, there was like  
9 600 references to the use of biphosphonates and other  
10 drugs for bone loss in both prostate cancer and in  
11 breast cancer. And so I won't pull out of the  
12 references here.

13 So I was rather surprised by the lack of  
14 discussion at all on that point, both in the  
15 presentations this morning -- and for that reason I  
16 feel like -- we had a lost -- somebody had a lost  
17 opportunity here to find out more about how this drug  
18 might have compared to some other drugs that are  
19 already out there that are being used in cancer  
20 patients, and we were given no data and no commentary  
21 about it all.

22 So in all of the next questions, I feel like

1 I know how I'm going to vote.

2 DR. CARSON: Dr. Mortimer?

3 DR. MORTIMER: But the claim was approved  
4 for those indications and they are not -- but still  
5 they're being used off label.

6 DR. ROSEN: Let's hear this again. So there  
7 is an approval for zoledronic acid. There is not an  
8 approved --

9 DR. MORTIMER: No.

10 DR. ROSEN: So they're not incorrect in  
11 stating there are no approved drugs for the treatment  
12 of --

13 DR. MORTIMER: They're absolutely correct,  
14 but there are drugs that are being used in this  
15 setting that are being used off label and are being  
16 covered by insurance.

17 MR. GOOZNER: This is Merrill Goozner. Let  
18 me underscore that I was very curious about that and  
19 so I went to the literature. I got no less than 691  
20 references, okay, on a PubMed search that looked at  
21 bone loss, cancer and biphosphonates.

22 DR. ROSEN: I understand. I'm just trying

1 to appreciate from the sponsor's point of view what  
2 they were trying to do and how they got their guidance  
3 in terms of this. So the concept was could they  
4 prevent bone loss in these individuals on aromatase  
5 inhibitors in breast cancer, correct? And if that's  
6 correct, then they did fulfill what they were asked to  
7 do.

8 DR. BUZDAR: Yeah, but I think the thing is  
9 that bone loss is not the major thing. The patients  
10 already have a fatal disease, breast cancer. They are  
11 getting aromatase inhibitor to prevent recurrence and  
12 there are a number of other options to reverse the  
13 bone loss in these patients, which are at least having  
14 no adverse outcome on the disease process itself.  
15 Over here you have a therapy which has been evaluated  
16 in a limited patient population, which may have -- at  
17 least we can say may have adverse outcome. So I think  
18 we have to be cautious.

19 DR. CARSON: I think it's important to  
20 remember that there is a lot of data, certainly on the  
21 Internet, certainly in PubMed, that are associated  
22 with a lot of different treatments. But our mission

1 here today is really to look at the information that  
2 we have at hand about one particular treatment and not  
3 really consider it among options, but rather consider  
4 it as does this drug have a favorable risk benefit  
5 ratio itself? Not compared to anything else, but  
6 rather does it have a favorable risk benefit ratio.

7 DR. EMERSON: And just to make the  
8 distinction, though, I like the way this question was  
9 worded, have they demonstrated a favorable risk? So  
10 it's not the question of does it have one but also do  
11 we have that demonstrated?

12 DR. CARSON: Isn't that the same?

13 DR. EMERSON: No. There can be a favorable  
14 risk benefit ratio that has been demonstrated. There  
15 can be one that's favorable that has not been  
16 demonstrated.

17 DR. CARSON: Well, that's true.

18 DR. EMERSON: Or that it could have been  
19 demonstrated that there isn't one. Somebody was  
20 complaining about double negatives, but that's my  
21 life.

22 DR. CARSON: Any other discussion?

1           DR. ROSEN: I hate to prolong this, but I  
2 just need some reassurance about the data in this  
3 particular trial about progression of malignancy in  
4 the breast cancer trial. So can somebody reinforce or  
5 reiterate for me, or let's look at the slides again?

6           Was there a statistically significant  
7 increase in cancer risk or --

8           DR. EMERSON: I believe we don't have any  
9 data on this trial. Where we did have data was in the  
10 PMO treatment study. There were six patients who  
11 progressed in that study who'd had that. So that was  
12 in the other study. It was not in this one, yes.

13          DR. ROSEN: Any statistical data that there  
14 is progression of disease in this study?

15          DR. CARSON: I think this is a very  
16 important point. And I want to ask the sponsor if we  
17 can quickly just come to the point and show us any  
18 data that you have regarding the progression of --

19          Do you have a slide that you can show us?

20          DR. DANSEY: We do.

21          DR. BUZDAR: Key thing will be to see number  
22 of recurrences on this subset.

1           DR. DANSEY: So as you are aware, this is a  
2 bone loss trial. It was set up specifically in women  
3 with osteopenia to measure outcomes from BMD. And we  
4 did as part of the due diligence for collecting  
5 adverse events, track the outcomes. Now bear in mind  
6 this is a low risk population, essentially is cancer  
7 survivors. They've completed the adjuvant therapy,  
8 and so the risk of progression is low. So when we  
9 review the information at a clinical level, we were  
10 able to determine that there were four subjects on  
11 denosumab and three subjects on placebo during the  
12 treatment phase for two years in which the denosumab  
13 was administered that we have clear evidence of the  
14 development of metastatic disease.

15           Then in the off treatment, that is the two  
16 year follow up, which is not yet complete, we see two  
17 subjects denosumab and two on placebo. There was only  
18 one new cancer, which was a gastric cancer. It was on  
19 the placebo.

20           DR. CARSON: So this two years on the drug  
21 and then 120 days after discontinuation.

22           DR. DANSEY: The term 120 days --



1 essentially it's a cut off data during that two year  
2 period. So it's not the complete two years, but it's  
3 a substantial amount of the information. We provided  
4 that information to the agency for follow up for  
5 safety information.

6 DR. CARSON: Okay.

7 DR. GULLEY: And how does this differ --

8 DR. CARSON: Thank you. I'm sorry.

9 Dr. Gulley?

10 DR. GULLEY: How does this differ with what  
11 the FDA presented which was --

12 DR. COLLINS: Right. Slide 74.

13 DR. GULLEY: Yeah.

14 DR. COLLINS: Slide 74.

15 DR. GULLEY: Yeah, they had nine on  
16 denosumab and five on placebo.

17 DR. CARSON: We'll get that.

18 Can we get FDA Slide 74 up?

19 DR. ROSEN: This is just in the 135 Study is  
20 all we're talking about in this case.

21 DR. CARSON: Whose slide is this?

22 Dr. Kehoe, is this your slide?

1                   Oh. Is this the slide you wanted Dr.  
2   Gulley? This isn't the slide you wanted is it? There  
3   it is.

4                   DR. COLLINS: So does this mean -- this  
5   slide, in Trial 135, this talks about imbalance in  
6   metastatic events. So these were breast cancers that  
7   were non-metastatic to start with but progressed to  
8   metastatic disease in the course of the study.

9                   Is that what this represents?

10                  DR. DEMKO: Yes. And also what I did was  
11   drill down, and even if it didn't say metastasis as  
12   the first word in the event, it could have said breast  
13   cancer metastatic, breast cancer progression, and  
14   metastasis. And that's how I counted the numbers,  
15   which is why they're somewhat higher than the sponsors  
16   numbers.

17                  DR. JOHNSON: Is this on both the prostate  
18   and the breast cancer combined?

19                  DR. DEMKO: The first one is Trial 135, the  
20   breast trial.

21                  DR. JOHNSON: Oh, I see. Okay, sorry.

22                  DR. DEMKO: And it's five in placebo and

1     nine for denosumab, and then Trial 138, the prostate  
2     trial is the second line.

3             DR. CARSON:   Dr. Emerson?

4             DR. EMERSON:   And not being prejudiced by  
5     too much knowledge on the subject, but both breast  
6     cancer and prostate cancer metastasize readily to the  
7     bone, due to characteristics of those sorts of  
8     cancers.  And so it is just this thing of -- there is  
9     a question to answer here and it just hasn't been  
10    answered yet.

11            I, in my heart of hearts, sincerely hope  
12    that actually what the sponsor is hoping for is that  
13    actually this is protective against bone metastases.  
14    I hope that that's true.  It just hasn't shown up and  
15    I might put a little bit of money on it, but not very  
16    much.

17            DR. BUZDAR:   Yeah, but the data which the  
18    FDA slide shows, it's the other way around;  
19    numerically, if the numbers are in the wrong  
20    direction.

21            DR. ROSEN:    If we could get some  
22    clarification on it.

1 DR. CARSON: I'm sorry.

2 Dr. Pazdur?

3 DR. PAZDUR: I'd like to just make a comment  
4 here. I think all you can say here is that these are  
5 descriptive. Okay? Somebody's asking are these  
6 statistically significant? It's impossible. These  
7 studies were not designed to put a p-value on these  
8 numbers here. They were not a hypothesis that was  
9 being tested.

10 Here again, you see what you get. And Aman  
11 is correct that you have a difference here, and  
12 unfortunately it's in favor -- or against, rather, the  
13 tested drug. The other information regarding  
14 progression events, I would urge a great deal of  
15 caution of interpreting any progression events unless  
16 we were very confident that these patients were  
17 assessed at the same time.

18 We have had numerous discussions on our  
19 Oncology Committee about time to progression and  
20 progression free survival, which is a very soft  
21 endpoint. And if this endpoint wasn't even stipulated  
22 as how frequently patients were being assessed, it's a

1 very muddy endpoint to be making any comments. So in  
2 essence, all you could say is, important signal; needs  
3 more data.

4 DR. CARSON: Any other comments, questions  
5 by the committee?

6 Okay, so let's vote on question 3A. Is a  
7 favorable risk benefit ratio demonstrated for  
8 denosumab for the treatment of bone loss associated  
9 with hormone ablation therapy in women with breast  
10 cancer receiving aromatase inhibitors? And now our  
11 favorite part, we get to vote electronically.

12 Okay. We got it.

13 The two members of the committee voted yes,  
14 and 13 voted no. So let's go back to this side and  
15 begin with your name and vote.

16 MS. SOLONCHE: Martha Solonche. I voted no  
17 because I have concerns about the development of new  
18 neoplasms and recurrence. And I say that as a three-  
19 time cancer survivor. And I'm also concerned about  
20 the risk of multiple adverse effects.

21 DR. GULLEY: James Gulley. I voted no,  
22 because most of the data did not look at treatment for

1     this group of patients.

2                 DR. RICHARDSON:   Ron Richardson.   I voted  
3     no, and I don't know whether to invoke Dr. Emerson or  
4     Bill Clinton, but I was hung up on the word  
5     "demonstrated".

6                 DR. MORTIMER:    I voted no, because an  
7     increase in T-score didn't translate to anything  
8     meaningful from a risk standpoint and weighing that  
9     against the potential risks is worrisome.

10                DR. CARSON:    Would you say your name, and  
11     repeat your vote, please?

12                DR. MORTIMER:   Oh, sorry.   Joan Mortimer.  
13     No.

14                DR. BUZDAR:    Buzdar.   I voted no because of  
15     the safety concern in this subset of patients and  
16     slightly in the wrong direction, i.e., the increased  
17     risk of the recurrence in small number of patients  
18     which have been studied.   So we don't know how safe is  
19     this molecule to be given to patients with established  
20     cancer, even though it might be a micrometastatic  
21     setting.

22                DR. MARGOLIS:   David Margolis.   I was one of

1 the few who voted yes. I think that it probably does  
2 prevent bone loss in a disease that for many is  
3 becoming more and more of a chronic disease, but I do  
4 agree that there are some concerns about long-term  
5 safety. I'm just not sure that the current study  
6 actually shows that there's a problem with recurrence  
7 of breast cancer.

8 DR. NELSON: Larry Nelson. I voted no,  
9 because of concerns about need for more data about how  
10 this affects their primary disease.

11 MR. GOOZNER: I'm Merrill Goozner. I voted  
12 no. To approve this drug for use in this patient  
13 population would put it at the head of the class, when  
14 there's a standard of care that apparently -- or close  
15 to a standard of care that's already out there, where  
16 we don't really have good information about, much less  
17 have good information about the real risks of this  
18 drug. So I think that that would be a terrible,  
19 terrible mistake.

20 DR. JOHNSON: Julia Johnson. I voted no. I  
21 thought that this study was well done to show a  
22 decrease in bone loss but didn't really show the

1 prevention that they were looking for. I'm sorry --  
2 the treatment they were looking for.

3 DR. CARSON: Carson. I voted no because I'm  
4 concerned about the data about long-term safety of  
5 recurrences and metastasis in a disease that goes to  
6 bone and what effect remodeling might have on that.

7 DR. EMERSON: Scott Emerson. I voted no for  
8 the reasons I've stated earlier.

9 DR. BENNETT: John Bennett. I voted no  
10 because I'm concerned about the progression of the  
11 primary disease, which would be a lot worse than  
12 having soft bones.

13 DR. UZEL: Gulbu Uzel. I voted yes, because  
14 I think imbalance is not the same thing as statistical  
15 significance. I acknowledge concerns, but that was my  
16 vote.

17 DR. ROSEN: No. I voted no, but I'd like to  
18 have an editorial comment. And that is that I'm  
19 afraid that the guidance provided to the sponsor was  
20 not appropriate to the question that was asked. This  
21 is powered for bone density. It's not powered for  
22 this kind of outcome that we're looking for. So they



1 did the study right. They showed an effect. They  
2 didn't have the power to do it. But that to me is a  
3 breakdown between the sponsor and the FDA.

4 DR. COLLINS: Collins. I voted no and echo  
5 Dr. Rosen's response.

6 DR. CARSON: Dr. Rosen, could you state your  
7 name and your vote.

8 DR. ROSEN: And take back the statement too?

9 DR. CARSON: I think we heard it.

10 DR. ROSEN: Cliff Rosen, and I voted no.

11 DR. CARSON: Okay. Any other statements  
12 before I summarize?

13 DR. ROSEN: I think I've got myself in  
14 enough trouble.

15 DR. CARSON: Okay. To summarize, the  
16 committee has voted no against a favorable risk  
17 benefit ratio demonstrated for the drug in the  
18 prevention of bone loss associated with hormone  
19 ablation therapy in women with breast cancer. I'm  
20 sorry. Let me -- I made a mistake.

21 It's no against a favorable risk benefit  
22 ratio demonstrated for denosumab for the treatment of

1 bone loss associated with hormone ablation therapy in  
2 women with breast cancer receiving aromatase  
3 inhibitors. The consensus seems to be that the  
4 concern for long-term safety data in these women was  
5 not demonstrated in the information provided.

6 Let's move on to question 3B. And now,  
7 again, is a favorable risk benefit ratio demonstrated  
8 for denosumab for prevention of bone loss associated  
9 with hormone ablation therapy in women with breast  
10 cancer receiving aromatase inhibitors. And this is  
11 again, the same question, but prevention rather than  
12 treatment. Let's begin the discussion.

13 Dr. Mortimer?

14 DR. MORTIMER: So I guess I'd have to say  
15 yes, it does increase your bone density. What's  
16 hanging out there is does it matter, and I'd say it  
17 doesn't matter.

18 DR. CARSON: Yes?

19 DR. BUZDAR: Yeah, I think the question is  
20 exactly the same. Over here the question you have to  
21 keep in mind is the risk benefit ratio, they have not  
22 established and shown that it is safe, because there

1 are fewer additional recurrences in the patients who  
2 got the antibody treatment compared to the patients  
3 who got placebo. So even though you change the bone  
4 density -- but I think you may be having an adverse  
5 outcome, and I would say that it will be wrong to  
6 support that statement.

7 DR. CARSON: Any other comments? Many of  
8 the issues that we've heard before are still the same;  
9 demonstrated, and then can you choose the patients who  
10 have osteopenia who would be provided benefit for  
11 osteoporosis in fracture. And they remain the same in  
12 this question.

13 Any other discussion? Okay, let's vote.

14 I'm told the flashing lights do not go off,  
15 but you do need to press yes, no or abstain.

16 How'd we do? Oh, at least the committee's  
17 getting better. There was 14 of the committee voted  
18 against and there was one abstention. So let's begin  
19 with Dr. Collins.

20 DR. COLLINS: Well, I mean I think if one  
21 voted no to 3A and you extend the logic, you have to  
22 vote no to 3B and again offer the same reasons.

1 DR. ROSEN: Dr. Rosen. I agree with  
2 Dr. Collins. I voted no.

3 DR. UZEL: Dr. Uzel. This is the same  
4 reason that I voted abstain, because I voted yes for  
5 the first reason, first question.

6 DR. BENNETT: Dr. Bennett. I agree with  
7 Dr. Collins and I voted no.

8 DR. EMERSON: Scott Emerson and I agree with  
9 the chorus over to my left.

10 DR. CARSON: Carson, and I voted no for the  
11 same reason I voted no for the last question.

12 DR. JOHNSON: Julia Johnson and I voted no.

13 MR. GOOZNER: Merrill Goozner. I voted no.

14 DR. NELSON: Larry Nelson and I voted no for  
15 the same reason as before.

16 DR. MARGOLIS: David Margolis. I voted no.  
17 I think treatment and prevention are different and the  
18 risks aren't well enough stated.

19 DR. BUZDAR: Buzdar. I vote no. I think  
20 the sponsor needs to show that it has a better  
21 therapeutic index and has more favorable profile in  
22 this subset of patient population. And up to now, the

1 data is not in support of it.

2 DR. MORTIMER: Joan Mortimer. I voted no.

3 DR. RICHARDSON: Ron Richardson. I voted  
4 no.

5 DR. GULLEY: James Gulley. I voted no.

6 MS. SOLONCHE: Martha Solonche. I voted no.

7 DR. CARSON: Okay. Let's move on to  
8 question 4. Is a favorable risk benefit ratio  
9 demonstrated for denosumab for the treatment of bone  
10 loss associated with hormone ablation therapy in men  
11 with prostate cancer receiving androgen deprivation  
12 therapy? So essentially the same question as 3 but  
13 for men with prostate cancer.

14 Let's open the discussion.

15 Dr. Collins?

16 DR. COLLINS: Could we have the opportunity  
17 to briefly review the data again as we did before with  
18 the breast cancer? Both here, though; not only,  
19 slide 74 from the FDA but also Amgen's slides in terms  
20 of fracture prevention as well.

21 DR. CARSON: For this group?

22 DR. COLLINS: Yes.

1           DR. CARSON: Okay. Would you share those  
2 with us again? And while you're doing that, maybe  
3 Dr. Emerson, are you able to ask yours?

4           DR. EMERSON: Yes, in terms of looking at  
5 that and the number needed to treat in this group,  
6 that if we take that face value, I computed that it  
7 would be about 50 in order to prevent one fracture of  
8 any type in this population, a much lower rate of  
9 fractures in this particular population with, again,  
10 my fears that saying this is a cancer that is prone to  
11 bone activity and we haven't really looked at what  
12 it's doing. And so all my same disclaimers about the  
13 breast, but I just don't think it's been demonstrated.

14          DR. CARSON: Okay, please go ahead.

15          DR. SMITH: If you'd bear with me for just a  
16 moment, I think it's worth pointing out that there's  
17 been no prior large fracture prevention study in men  
18 in any setting. And when we designed this trial in  
19 2004, we were faced with the dilemma of identifying a  
20 patient population at somewhat increased risk for  
21 fracture, so that we could demonstrate a benefit but  
22 really having no prior large database on which to base

1 the patient selection.

2 I believe the data that we presented shows  
3 that we were successful and that we've demonstrated  
4 robust benefit on BMD, and as you show here, a  
5 reduction in vertebral fractures, that it was of  
6 comparable relative magnitude to that shown in the  
7 large PMO study.

8 The number needed to treat, of course, is  
9 very dependent upon the baseline risk for fracture.  
10 And as I'd indicated, there was no firm basis on which  
11 to identify patients in the past. And there's really  
12 no other therapeutic to compare these results to,  
13 because there's never been a large fracture prevention  
14 study done in men in any setting, and certainly not  
15 done in hypogonadal men.

16 The studies that were eluded to in androgen  
17 deprivation therapy or in HALT in other settings are  
18 all very small studies typically involving a dozen  
19 patients to, at most, 200, most with one year of  
20 follow up. This is the largest study completed to  
21 date with 1,500 patients approximately and three years  
22 of follow up. And it's nice to see, I think, that the

1 fracture benefit seen is very comparable to that what  
2 we're seeing in the treatment study in PMO.

3 DR. CARSON: Okay. So this is the decrease  
4 in new vertebral fractures.

5 DR. SMITH: Correct.

6 DR. CARSON: And Dr. Johnson?

7 DR. JOHNSON: Did you look at non-vertebral  
8 fractures?

9 DR. SMITH: We do have that data. And as  
10 the endocrinologists on the committee could speak to  
11 much better than I can, to show BMD benefit requires  
12 dozens to perhaps a few hundred patients. To show a  
13 reduction in vertebral fractures requires perhaps a  
14 few thousand patient years of follow up as we had in  
15 this study. To show a significant reduction in non-  
16 vertebral fractures or any clinical fractures, we  
17 believe would require probably many more thousands of  
18 patient years of follow up.

19 DR. CARSON: Do you have the data for non-  
20 vertebral fractures? Can we see that?

21 DR. SMITH: Well so this is any -- this is  
22 any fracture outcome showing a trend in favor of



1     denosumab. It didn't reach statistical significance,  
2     and then you see the endpoint of multiple vertebral  
3     fractures at any site showing a reduction in benefit  
4     of denosumab.

5             DR. CARSON: And then I believe there was  
6     also a --

7             Dr. Collins, you also wanted to see the  
8     metastatic cancer risk.

9             Do you have that as well? No?

10            DR. COLLINS: Well it was the same FDA slide  
11     we saw before. If we could see it again.

12            DR. SMITH: Yeah, so it's that same FDA  
13     slide that was shown earlier in the discussion, the AI  
14     treated patients.

15            DR. CARSON: Oh, Slide 64?

16            DR. SMITH: I believe Dr. Pazdur made a very  
17     important comment in that ascertainment of outcomes  
18     like disease progression by AEs are very problematic  
19     and potentially unreliable because of the issue of --  
20     there's no pre-specified time of ascertainment of  
21     these types of outcomes.

22            So if I could have -- so as you can see,

1    there was a numerical imbalance that was in favor of  
2    placebo in this, but we also very carefully looked at  
3    in a pre-specified manner at specified time points, a  
4    disease progression by three metrics -- PSA  
5    progression, bone scan progression and then we have  
6    overall survival data.

7                So this PSA data that you'll see was all  
8    centrally measured. It was done at six month  
9    intervals. There was very careful ascertainment of  
10   the PSA outcome, and as I described earlier, at each  
11   of the time points, there is no suggestion of worse  
12   cancer progression by PSA criteria that would suggest  
13   a detrimental effect of denosumab.

14               Now we also looked at bone scan progression,  
15   and, again, this has the strength of being done at  
16   pre-specified time points, including end of study.  
17   And here you see that there's really no deleterious  
18   effect of denosumab in terms of bone scan progression  
19   with really overlapping curves.

20               Further supporting the safety of denosumab  
21   in this patient population is the overall survival  
22   data, showing that there's no deleterious effect of

1     denosumab in overall survival.

2                     So I think by several important metrics, PSA  
3     progression, bone state progression and overall  
4     survival, that there's no suggestion, there's no hint  
5     that denosumab has any deleterious effect on cancer  
6     control. And as I'd alluded to earlier, we actually  
7     believe that denosumab may delay or prevent disease  
8     progression. And there's an ongoing trial, it's fully  
9     approved, and that study will look at the primary  
10    outcome of bone disease progression or death as the  
11    primary outcome. The study is fully approved and we  
12    expect to have that data relatively soon.

13                    DR. COLLINS: So what's the difference in  
14    dose between the study you just spoke of and this?

15                    DR. SMITH: Yes. So this of course was an  
16    osteoporosis study and we have the disease progression  
17    data as I presented. The dose and schedule in the  
18    metastasis prevention study, the 147 Trial is 12 times  
19    higher. So it's the same dose and schedule as is  
20    being used in the treatment of metastatic bone  
21    disease.

22                    DR. COLLINS: So will we really be able to

1 extend those data to this population, you think?

2 DR. SMITH: Well I think these are the data  
3 that we can speak to now about the theoretical concern  
4 that denosumab would worsen cancer progression, right?  
5 So I think that stands for itself. The hypothesis  
6 we're testing in the other trial is actually that  
7 it'll have a favorable effect.

8 Now if in fact there was a deleterious  
9 effect, we'd of course expect the signal to be really  
10 quite substantial in a treatment at 12 times the  
11 dosing schedule.

12 DR. CARSON: Yeah, unfortunately we do have  
13 to limit our discussion to the data that was presented  
14 in the studies that are completed.

15 DR. COLLINS: Right. But then there seems  
16 to be a discrepancy between your bone scan data and  
17 the FDA data in terms of -- how did you assess  
18 metastatic disease in this prostate cancer population  
19 if it wasn't by bone scan?

20 DR. SMITH: Well I believe that -- I'll let  
21 FDA speak for themselves, but the data for adverse  
22 events is ascertained just as their investigator

1 reports using MedRA terms. And as Dr. Pazdur nicely  
2 pointed out, there are limitations to such data. In  
3 fact, when we drilled down into this data, at least a  
4 third of the so-called disease progression, adverse  
5 events had no corresponding PSA progression, which as  
6 a medical oncologist who only takes care of men with  
7 prostate cancer is really kind of an untenable  
8 category that there'd be disease progression with no  
9 corresponding PSA progression.

10 So I think it just points out to the fact  
11 that there's limits to the reliability of cancer  
12 progression as ascertained by adverse event data.

13 DR. PAZDUR: And let Dr. Pazdur point out  
14 one more time these are exploratory analyses, and I  
15 think we have to be very cautious in making and  
16 definitive conclusions on this. Here again, I think  
17 more data is necessary here, really, to be making  
18 exploratory and descriptive analyses.

19 DR. COLLINS: But I think since we have to  
20 decide today, and given the data we have to work with,  
21 I find the sponsor's data in regard to this probably  
22 stronger and generally comforting.

1 DR. CARSON: Dr. Rosen?

2 DR. ROSEN: Thank you. I'd like to explore  
3 with the sponsor, if it's okay, the vertebral  
4 fracture -- I mean the total fracture incidence in  
5 this population with prostatic cancer patients.

6 So the baseline characteristics were  
7 23 percent of these men had prevalent vertebral  
8 fractures and you have a clear trend towards reduction  
9 in total fractures and a reduction in new vertebral  
10 fractures. The placebo rate of fractures was  
11 7 percent.

12 Is that higher than the rate in, let's say,  
13 Mr. Osseer (ph), for a 75-year-old man with a 7 to 7  
14 and a half percent fracture rate per year?

15 What I'm trying to get at is whether this  
16 group of men is at high risk for a fracture, either  
17 vertebral fracture or other fracture. So how does the  
18 prevalence of fracture in this population correspond  
19 to prevalence in a normal male population of 75 years  
20 of age without prostate cancer?

21 DR. CARSON: Dr. Mortimer?

22 DR. MORTIMER: I mean there is no literature

1   that demonstrates that men with prostate cancer have  
2   lower bone densities than do normal men in the  
3   population without prostate cancer.

4               DR. ROSEN:  Right.  I guess what I'm trying  
5   to get at is whether or not this is a -- there's a  
6   high rate of fracture -- a higher rate of fractures in  
7   men with prostate cancer that have -- 25 percent of  
8   them have prevalent vertebral fractures.  So this  
9   represents a high risk -- I guess what I'm trying to  
10   say is, is this a high risk group of individuals who  
11   require interventions?

12              DR. SMITH:  I believe so for several  
13   reasons.  I mean, as you pointed out, this patient  
14   population is at substantially increased risk.  About  
15   a quarter of the patients had prevalent vertebral  
16   fractures, which interestingly enough is not too  
17   dissimilar from the 216 PMO population, right?  I  
18   think it was pointed out that the T-scores were  
19   relatively normal, but I think it's also worth noting  
20   the usual limitations of screening for osteoporosis in  
21   older men, particularly with limitations of spinal  
22   BMD.

1           But I'd also like to point out a couple of  
2 other things, that 80 percent of the men had either  
3 osteopenia or osteoporosis, at at least one measured  
4 skeletal site. So they're a relatively ill population  
5 from a fracture risk perspective.

6           The other point is that the impact of the  
7 androgen deprivation therapy on fracture risk is  
8 largely explained by bone, but there are other issues,  
9 including muscle loss, obesity and frailty, which we  
10 believe placed them at particularly high risk for  
11 fracture.

12           DR. ROSEN: Yeah, I'm not interested in bone  
13 density. I'm interested in fracture risk, and it  
14 sounds like due to androgen deprivation, maybe Steve  
15 can help us on that versus normal males.

16           DR. CUMMINGS: Seven percent vertebral  
17 fracture risk over the course of two years is somewhat  
18 higher than seen in Mr. Osser, other male studies.  
19 You're exactly right, Cliff. But that's in part  
20 because these men are losing bone more rapidly in the  
21 absence of not only testosterone but estrogen.  
22 That's, you know, the controls preservation of bone.



1     So yes, they're at somewhat higher risk for the number  
2     of fractures.

3             DR. ROSEN:   So I guess one of things too --  
4     so when did these men enter the study in terms of  
5     castration.  Had they been castrated for a period of  
6     time?  Did they start treatment when they started  
7     androgen deprivation therapy?  And also, what's the  
8     expected length of androgen deprivation therapy?  Are  
9     we talking about a group who are only going to treat  
10    for three years or a group who are going to treat for  
11    10 years, when we don't know the ten year risk -- that  
12    sort of thing.

13            DR. SMITH:   Well again, we know what we  
14    know, and this is the first large fracture prevention  
15    study in men.  It was required that the patients would  
16    go on androgen deprivation therapy with the intention  
17    of remaining on therapy for the duration of the trial.  
18    So most of these are going to be salvaged patients,  
19    patients who, by the way, do very well, which is why  
20    we're concerned about these issues related to  
21    survivorship.

22            The median time on androgen deprivation

1 therapy at study entry was approximately three years  
2 in both groups, so these were mostly patients  
3 receiving long-term treatment.

4 DR. CARSON: Dr. Buzdar --

5 Oh, I'm sorry. Do you want to finish about  
6 this?

7 DR. ROSEN: Not knowing the prostate cancer  
8 field well, these people were on androgen deprivation  
9 therapy for three years when they entered and will  
10 they be on androgen deprivation therapy for a lifetime  
11 or --

12 DR. SMITH: Yes, so there is different  
13 contexts for which the therapy is used, but a very  
14 common scenario is for patients with recurrent  
15 disease, which represented most of these patients,  
16 it's going to a lifelong androgen deprivation therapy.

17 DR. CARSON: Thank you.

18 Dr. Buzdar?

19 DR. BUZDAR: Yeah, I have never treated  
20 prostate cancer in my life, but the thing which I want  
21 to get some clarification on is that looking at the  
22 FDA interpretation of the same data, there is almost

1 50 percent increase in the risk of progression of the  
2 disease.

3 Question is who to believe. Is the sponsor  
4 more accurate than FDA more accurate over here?  
5 Because 40 events versus 60 events, which are disease  
6 progression on the antibody therapy.

7 DR. ROSEN: Well my interpretation, as I  
8 said before, is that the sponsor's data strike me as  
9 stronger. If it's not there on bone scan, it's  
10 probably not there.

11 DR. CARSON: Do you want to comment on just  
12 the discrepancy of the -- where the difference is.

13 DR. DEMKO: It's the same situation. It's  
14 with MedRA, and when you drill down to the lowest  
15 level, that's not a verbatim term, you can see terms  
16 such as metastasis versus prostate metastasis versus  
17 prostate progression, and I included those in the  
18 numbers.

19 DR. CARSON: Is that clear?

20 Okay.

21 Dr. Mortimer?

22 DR. MORTIMER: Again, the other issue of

1 drugs approved for -- I mean these -- in the standard  
2 of care presently ongoing, these men would not be  
3 untreated. So the fact that they have low bone  
4 density, they would again be treated with an IV  
5 biphosphonate.

6 DR. ROSEN: I don't know that that's the  
7 case. There is no standard of care in the treatment  
8 of these guys. We just went through this whole group  
9 with our prostate cancer treatment at the NIH, and  
10 it's really -- you're hard-pressed to find anything  
11 that resembles a standard of care.

12 DR. CARSON: Well again, let me remind you  
13 that this is not a comparison trial or it's really  
14 limited to the data that we have on hand rather than  
15 comparing it head on head to another drug.

16 Okay. Any other panel questions,  
17 discussions, comments?

18 Dr. Rosen?

19 DR. ROSEN: Again, I have to come back to  
20 the MedRA analysis, and we really need some  
21 clarification on what MedRA's telling us, because  
22 we're getting this contrasting story, and I still

1     don't quite understand.

2                   When you say you drill down, what are you  
3     looking at? Are you looking at what's recorded or are  
4     you looking at case reports? So these are adverse  
5     events that the sponsor has submitted?

6                   DR. DEMKO: This is the sponsor's data and  
7     it's grouped according to system organ class, which is  
8     one of the levels of the MedRA hierarchy along with  
9     preferred term, which is a lower level of the MedRA  
10    hierarchy. And under the neoplasms class, there is an  
11    entire listing of reported terms that are reported by  
12    the investigator that are then coded by the sponsor,  
13    taking their verbatim term to a lower level term that  
14    then turns into all the different levels of the  
15    hierarchy automatically.

16                   In some cases, I did go back where they were  
17    available and looked at the case report forms or any  
18    narratives that were available to try to confirm that  
19    these were indeed cases of metastasis. However, I did  
20    not look at every single case.

21                   DR. CARSON: Any other --

22                   Yes, Dr. Margolis?

1           DR. MARGOLIS: To maybe muddy it more,  
2   having served on numerous data safety monitoring  
3   boards where you constantly get report surveys, the  
4   MedRA data, that you then have to check with SAE  
5   reports and case report forms. You know MedRA tends  
6   to be what somebody checks a box on or uses some  
7   descriptor. They don't necessarily correspond to what  
8   you find out when you really look carefully.

9           It's a very different assessment and it's  
10   not fair to say it's the same data, which a few people  
11   have implied, as if it were a primary outcome, if you  
12   drawing a blood test, taking an x-ray, measuring  
13   something as part of the normal protocol. It's a  
14   different assessment.

15          DR. CARSON: Dr. Richardson?

16          DR. RICHARDSON: I got a chance to invoke  
17   Dr. Emerson, Bill Clinton; now I get a chance to  
18   invoke Dr. Pazdur in saying that we can't read too  
19   much into this. I mean one question is just how does  
20   this group of prostate cancer patients fit with the  
21   practice in the States. Fifty percent of these people  
22   had hormonal treatment as their primary therapy. Only

1 25 percent had surgery, 25 percent had radiation, the  
2 rest were treated hormonally.

3 I'm surprised they could find this number of  
4 patients with a PSA less than five treated on hormonal  
5 treatment to get into this study. So I think there  
6 are some real limitations as to how we're looking at  
7 this group and what the biology of this group is  
8 versus the folks that are out there walking on Main  
9 Street.

10 DR. SMITH: May I comment?

11 DR. RICHARDSON: Please.

12 DR. SMITH: So I'm a medical oncologist,  
13 prostate medical oncologist. My practice is entirely  
14 prostate cancer. Androgen deprivation therapy of  
15 course is the mainstay of treatment for locally  
16 advanced as well as metastatic disease. My practice  
17 is full of prostate cancer survivors who presented  
18 with locally advanced non-metastatic disease who are  
19 long-term PSA remission patients. So these are  
20 patients who represent a large proportion of the  
21 nearly six-or-seven-hundred-thousand men on current  
22 androgen deprivation therapy. So this a very large

1 population of survivors.

2 DR. CARSON: Thank you very much for your  
3 comments.

4 DR. RICHARDSON: I see predominantly  
5 prostate cancer myself, and I would say that my  
6 population is substantially different. They have to  
7 be sick enough to get there.

8 DR. CARSON: Dr. Gulley, did you --

9 DR. GULLEY: Just back to the -- I think the  
10 difference between the MedRA analysis and the  
11 sponsor's analysis, I think clearly the prospectively  
12 designed and analyzed endpoints that were presented by  
13 the sponsor, I mean I would agree with Dr. Collins,  
14 that that's what we should be looking at, not at what  
15 may or not have eventually happened and with the cases  
16 in the MedRA.

17 DR. CARSON: Any other comments or summary  
18 statements? I'm afraid that we don't -- thank you.

19 Are there any other panel comments?

20 Okay. Are we ready to vote? Our favorite thing.

21 Is a favorable risk benefit ratio  
22 demonstrated for denosumab for the treatment of bone



1    loss associated with hormone ablation therapy in men  
2    with prostate cancer receiving androgen deprivation  
3    therapy? We do have one less voting member.

4                    Okay. The nine committee members voted yes,  
5    four voted no, and one abstained.

6                    So shall we go back to Ms. Solonche?

7                    MS. SOLONCHE: Martha Solonche. I  
8    abstained.

9                    DR. GULLEY: James Gulley. I voted yes. I  
10   think that the data set here was bigger and there's  
11   the availability of the secondary endpoint with the  
12   improvement in fracture risk. I think that that  
13   helped with assessing the risk versus benefit, and I  
14   thought there was a clear benefit here.

15                   DR. RICHARDSON: Ron Richardson. I voted  
16   no, mainly because I think at this point in time, the  
17   risks I think in this group haven't been completely  
18   elucidated. I think the benefits are modest. I think  
19   the thing to remember about many of these elderly men  
20   is that they've got lots of other co-morbidities that  
21   complicate this issue. And I think when you add some  
22   of these other concerns about safety into this, I

1 think the risk factors accumulate substantially and  
2 that's the basis for my voting no.

3 DR. MORTIMER: Joan Mortimer. I voted no  
4 for the reasons that Dr. Richardson said. I think the  
5 risks far outweigh the benefit here, even if the risk  
6 of cancer recurrence isn't defined for certain.

7 DR. BUZDAR: Buzdar. I voted no for two  
8 reasons. One is that there is evidence that, yes,  
9 there was a reduction on the vertebral fracture, but  
10 overall fracture reduction was not statistically  
11 significant. And also, I think looking at the FDA  
12 report, where there's almost 50 percent adverse impact  
13 on the disease progression, I think that is an  
14 important issue which means that they have not shown  
15 clearly that it has a better therapeutic index.

16 DR. MARGOLIS: David Margolis. I voted yes  
17 for my previously stated reasons.

18 DR. NELSON: Larry Nelson. I voted yes,  
19 because I thought this was a well-designed study. It  
20 followed 1,500 men for three years and prospectively  
21 looked at hard markers. But I have to add I have some  
22 concern. I couldn't vote yes for breast cancer as a

1     gynecologist, because why didn't they have a similar  
2     type of design for the breast cancer.

3             MR. GOOZNER: I voted no because I see some  
4     real risks here. And I also see that this is a  
5     patient population with cancer, and so it should be  
6     treated more like a cancer trial and not like a bone  
7     density trial in this case, especially when the  
8     company is already out there with this drug, testing  
9     it against cancers, because there is some hint it  
10    could work that way. It seemed to me that this is the  
11    way they should have gone with this trial, rather than  
12    simply going for a bone density indication.

13            The real risk, it seems to me here, is that  
14    if they were to get the bone density indication, that  
15    this drug will be widely used off label as a cancer  
16    therapeutic without evidence of really having benefit  
17    of that, and that strikes me as not really where we  
18    want to go. That was Merrill Goozner.

19            DR. JOHNSON: Julia Johnson. I voted yes.  
20    I did think that this was a strong study. It clearly  
21    did a lot better job at looking at the potential  
22    benefit of this medication for these cancer survivors.

1 And I was impressed by the fact that they were able to  
2 show no difference in the bone CTs or the PSA. That  
3 really made it much it a much stronger study than the  
4 breast cancer study.

5 DR. CARSON: And I, Carson, yes. And again,  
6 the same as Dr. Nelson and Johnson. And I'm so  
7 disappointed that I couldn't vote yes because there  
8 were no hard markers in the breast cancer study.

9 DR. BENNETT: Dr. Bennett, and I voted yes  
10 for all the reasons that the rest of you have well  
11 stated.

12 DR. UZEL: Gulbu Uzel. I voted yes in  
13 agreement with all the reasons mentioned before me.

14 DR. ROSEN: I voted yes, too, because I  
15 thought that it was a well-designed study and there  
16 was fracture efficacy. And these relatively low risk  
17 older gentlemen have significant morbidity from  
18 fracture, and I think we need to have a drug out there  
19 that reduces fracture.

20 DR. COLLINS: Collins. I voted yes, again  
21 in agreement with many of the statements said before,  
22 but I would like to add that it's a cautious yes with

1 concern still over safety and again emphasizing the  
2 need for the ongoing follow up studies. And again,  
3 concern that the 12 time dose metastatic prevention  
4 study -- that those data -- it's questionable whether  
5 they'll inform this group of patients at all.

6 DR. CARSON: Okay. The committee voted in  
7 favor of a favorable risk benefit ratio demonstrated  
8 for denosumab for the treatment of bone loss  
9 associated with hormone ablation therapy in men with  
10 prostate cancer receiving androgen deprivation  
11 therapy. And I think it was the consensus of the  
12 committee that there was a demonstrated efficacy in  
13 reducing a fracture in these men and as well as the  
14 committee felt that the long-term safety risk, or at  
15 least the safety risk demonstrated was -- showed with  
16 hard markers and that were not surrogate markers.

17 Let's move on to question 4B. Is a  
18 favorable risk benefit ratio demonstrated for  
19 denosumab for the prevention of bone loss associated  
20 with hormone ablation therapy in men with prostate  
21 cancer receiving androgen deprivation therapy? So  
22 once again, essentially a similar question to 4A,

1 except for the prevention rather than the treatment of  
2 bone loss. And let's open the discussion of the  
3 panel. So the same issues --

4 Dr. Rosen, go ahead.

5 DR. JOHNSON: Can I ask a question, though,  
6 of the osteoporosis experts? I mean I was amazed that  
7 the T-score on average was minus .36. So a pretty  
8 normal T-score for these gentlemen, but yet a number  
9 of them had fractures.

10 So is prevention different from this group?  
11 Because this was not what looked like a high risk  
12 group, but they had a number of fractures. I mean, my  
13 tendency is to say prevention is a hard thing to  
14 determine in terms of prevention of osteoporotic  
15 fractures. This group seems somewhat unique to me  
16 however.

17 DR. ROSEN: So I don't know, was that spine  
18 T-score or was it hip? Spine.

19 DR. JOHNSON: That was lumbar.

20 DR. ROSEN: Yeah, yeah. So generally  
21 those -- spine BMD goes up with age. They had  
22 advanced age at 75, so it's not as good a risk

1 predictor anyways in the age group over 65, but I  
2 would argue with a 23 percent prevalent rate;  
3 23 percent of them had vertebral fractures. That's  
4 pretty high for an older population of men. And the  
5 fact is, having been on hormonal ablation therapy,  
6 that puts them at high risk.

7           So I mean it highlights the issue that I  
8 think we got back to with prevention that BMD is not  
9 the end all to be all. And in this situation, you  
10 need clinical judgment to identify people at risk.  
11 And a male that is undergoing hormone ablation therapy  
12 is going to lose significant bone over a significant  
13 period of time.

14           DR. JOHNSON: So are you suggesting that men  
15 who are getting this treatment, probably do need  
16 prevention generally as a group?

17           DR. ROSEN: Well I think that most people  
18 who are on hormonal ablation therapy, most men are  
19 getting some form of treatment one way or the other in  
20 terms of biphosphonates. I think in most people that  
21 are being referred, we see it. They're on a  
22 biphosphonate, although the data on that isn't nearly

1 as strong as it is from this prevention trial.

2           So, I mean, when a patient comes in, I don't  
3 look at the bone density and say you're not at risk  
4 because your T-score is zero. I say, you could have  
5 been plus two and have lost 20 percent of your bone  
6 density over the six years of hormonal ablation  
7 therapy.

8           DR. CARSON: Dr. Collins?

9           DR. COLLINS: Yes. What I'm struggling with  
10 here is so -- I mean if the question is in this group  
11 of patients who have been on androgen deprivation for  
12 three years to start with and a third of them have  
13 osteoporosis because they have vertebral fractures,  
14 should that group be treated? Yes.

15           If I confine my thinking to that, it's  
16 clear. But if I have to extend to the guy whose just  
17 diagnosed with prostate cancer, and he's getting ready  
18 to go on androgen deprivation therapy, should he get a  
19 biphosphonate? Should he get this drug? I'm not sure  
20 where I stand.

21           DR. CARSON: Well again, we're asked to look  
22 at whether the data we have before us demonstrated



1     that this drug prevented bone loss.

2                 DR. ROSEN:   Can I just make a point -- and  
3     then the way the question is phrased, if they had gone  
4     back to some of the original questions, which were, is  
5     there a subgroup of individuals that are at high risk  
6     and had a favorable risk profile for prevention, that  
7     would be a little more comforting because Dr. Collins  
8     is right.  Otherwise, we open it up to say everybody  
9     who's started on ablative therapy is going to get  
10    treatment or everybody who's got -- initiated ablative  
11    therapy.  And it's not true that everybody gets  
12    therapy immediately with ablation nor that everybody  
13    loses bone with ablative therapy.  But if we identify  
14    those people at higher risk -- so I think the question  
15    is a little more global and maybe it should be more  
16    specific.

17                DR. CARSON:   Go ahead, Dr. Collins.

18                DR. COLLINS:   And I think Mr. Goozner's  
19    point is really well taken.  You can see it that a  
20    drug gets approved and then it gets given to people  
21    who -- to everybody.  And I guess that's not really  
22    our concern.

1           DR. CARSON: And I think that's probably  
2 why -- point well taken, Dr. Rosen. But I think  
3 that's probably why this question is quite global and  
4 quite inclusive, because it's closer to how clinically  
5 it gets used.

6           Dr. Mortimer? Oh, it's Dr. Buzdar?

7           DR. BUZDAR: Yes. I think the thing which  
8 we again have to keep in mind, that we are being asked  
9 is it a favorable risk benefit ratio, and I think that  
10 question has not been answered clearly. Because over  
11 here, the control arm is placebo. There are effective  
12 therapies. And then you see the slide that placebo if  
13 you -- in other words, did nothing, survival was  
14 identical. Outcome was identical, these patients who  
15 did not get any therapy. So I personally think that  
16 if you look at the other side of the coin, that maybe  
17 the answer is no.

18          DR. CARSON: Dr. Margolis?

19          DR. MARGOLIS: Sure. David Margolis. I  
20 think we need to be careful and think about what the  
21 study was designed to show and I think it was designed  
22 to show treatment, and many of these people were

1 fairly sick. It wasn't designed to look at somebody  
2 who's just initiating care. I also think it's  
3 important to realize, unless I'm forgetting the  
4 studies, that in every one of these studies, while the  
5 word placebo is being used, they were all treated with  
6 Vitamin D and calcium, which in some parts of this  
7 country and other countries is considered a therapy  
8 for osteopenia and osteoporosis.

9 DR. CARSON: Dr. Nelson?

10 DR. NELSON: Dr. Rosen, I wonder can you  
11 clarify for me. I thought hypogonadism was a major  
12 risk factor for osteoporosis. So why wouldn't you  
13 want to start somebody -- a male -- that we have this  
14 evidence. Why wouldn't you want to start him on this  
15 to prevent osteoporosis?

16 DR. ROSEN: Well, I mean I think there are  
17 other options, calcium and Vitamin D. Not everybody  
18 who gets hormone ablative therapy -- just like post-  
19 menopausal women, some women after chemotherapy don't  
20 lose bone. It's not an absolute. And what worries me  
21 is that it's clear that treatment of bone loss in  
22 question 4A, is the treatment of bone loss -- it's

1 established they have bone loss. We're treating  
2 those.

3           Here, we're preventing something that we're  
4 not sure is going to happen. I mean it's likely to  
5 happen, but it requires follow up. So what we do  
6 often with our men is say we'll repeat your bone  
7 density in two years and we'll see if you've lost  
8 bone. And not all of them do. So that's my concern  
9 about prevention versus treatment in this population.  
10 I don't think you can globally -- everybody's at risk  
11 with ablative therapy.

12           DR. NELSON: Right. Well, the reason I ask  
13 is say you have a patient like that and two years  
14 later you do their bone density and it's dropped a  
15 lot, but it's still not osteoporotic. Wouldn't you  
16 start treating then?

17           DR. ROSEN: Yes, I would. I would. I don't  
18 care what their absolute number is. If they've lost  
19 significant bone, I would treat them. And that's what  
20 question 4A is and that's why I was so insistent. But  
21 when we talk about prevention of something that may or  
22 may not occur, that's a different story.

1                   DR. NELSON: No, but I'm talking about -- it  
2 would still be prevention if they don't have  
3 osteoporosis yet, but they're on their way towards it  
4 based on your two years of observation. So my view  
5 would be, if you do get evidence that they're  
6 deteriorating, we should be able to use this as  
7 prevention before they get to osteoporosis.

8                   DR. MORTIMER: I'm sort of struck that the  
9 way the committee has sort of lined out are the  
10 oncologists are the folks that are worried about the  
11 increased risk. And I think I speak for my colleagues  
12 on either side of me, if there's any suspicion that  
13 your cancer is going to come back earlier, that is a  
14 risk that outweighs anything, especially since there  
15 are other therapies. And I suspect our cancer  
16 advocate would say the same. If there's any suspicion  
17 that there's an increased risk of cancer recurrence,  
18 it is not worth it and that is an incredible risk.

19                   MR. GOOZNER: Dr. Rosen, you made two  
20 comments. I'm curious. Earlier you said that there  
21 was no treatment and then you said we could give them  
22 biphosphonates. So which is it?

1 DR. ROSEN: -- established, there hasn't  
2 been a randomized trial is what I'm saying, of this  
3 degree to show that. That's all. That's what I was  
4 trying to say. That there's no FDA approved treatment  
5 currently for this. There are studies that suggest  
6 it, but there isn't a randomized controlled of this  
7 degree. That's all I was trying to establish. There  
8 clearly are treatments for bone loss in these  
9 individuals, and biphosphonates have been the first  
10 line therapy.

11 DR. CARSON: Dr. Kehoe?

12 DR. KEHOE: Yes. I just wanted to clarify  
13 for Dr. Nelson. If you recall the slide that we  
14 showed on the indications, for treatment of bone loss  
15 in men undergoing hormone ablation therapy, that  
16 included patients that were on therapy and had  
17 demonstrated significant bone loss. We would place  
18 those patients in a treatment category, not in the  
19 prevention category.

20 DR. NELSON: Even if they were not  
21 osteoporotic yet.

22 DR. KEHOE: Yes.

1 DR. CARSON: Dr. Uzel?

2 DR. UZEL: I had one comment. In the field  
3 of immunology and infectious disease, there are  
4 definite guidelines; what you do, what you treat, who  
5 you treat. We are discussing about approval of a  
6 medication in a field where -- in a subset of patients  
7 where there are no good guidelines.

8 How do you approach the patient, how do you  
9 -- what do you call high risk and who do you treat?  
10 What's the best effort to treat this patient? So you  
11 can see the dilemma between the members of the  
12 committee. And I guess I would like you to take  
13 consideration when making your decision, voting for  
14 this question. Just my comment.

15 DR. CARSON: Any other comments for the  
16 committee before we vote? Summaries? No. Okay.  
17 Let's vote.

18 Is there a favorable risk benefit ratio  
19 demonstrated for denosumab for the prevention of bone  
20 loss associated with hormone ablation therapy in men  
21 with prostate cancer receiving androgen deprivation  
22 therapy?

1           We did so well last time. Let's try again.  
2   If all the committee members could vote again. All  
3   right. Got it. Three committee members voted yes and  
4   eleven, no.

5           So if we would start with you, Dr. Collins?

6           DR. COLLINS: Collins. I voted no. I think  
7   it falls short when we consider prevention as opposed  
8   to treatment in that we aren't really entirely clear  
9   of the natural history in this disease and we have  
10   remaining questions about safety.

11          DR. ROSEN: I'm Dr. Cliff Rosen, and  
12   Dr. Mortimer scared me. And I think that I would  
13   have -- I would actually -- I think that her point,  
14   some of her points on the other side of the room from  
15   that group, that's always diametrically opposed to us,  
16   are correct. And I think when we talk about  
17   prevention, it's different than treatment. So the  
18   subtlety of the words are important, and I would not  
19   like to see a global indication for everybody to go on  
20   this until we're sure that the risk benefit is okay.

21          DR. UZEL: Gulbu Uzel. I voted no. I also  
22   gave into the oncologists, which is not usual for the



1    infectious disease team to give in to oncologists, but  
2    I agree that the risk safety concerns are unclear for  
3    this population.

4            DR. BENNETT:    John Bennett.    I voted yes.    I  
5    believe we have a population between 14 and 1,500  
6    patients.    And we've looked at disease progression  
7    with three different parameters. and it does not seem  
8    to me like there is a sizable risk.

9            How do we know what's safe?    It takes huge  
10   patient populations to know what's absolutely safe.  
11   But for the moment, I think this was safe enough for  
12   approval.

13           DR. CARSON:    Carson.    I voted yes.    I was  
14   convinced that this does prevent a drop in bone  
15   mineral density and those hard endpoints, again,  
16   convinced me of the relative safety.    And once again,  
17   as an obstetrician, gynecologist, I'm so sad to see  
18   this study not duplicated in women.

19           DR. JOHNSON:    Julia Johnson.    I voted no.    I  
20   thought in terms of prevention, as with the other uses  
21   of this medication, that that's a softer usage.  
22   Clearly, the men who were at high risk could use it

1 for treatment, but I want to wait a bit before we  
2 consider it for prevention.

3 MR. GOOZNER: I voted no. As I said  
4 earlier, I think that when you're treating cancer  
5 patients that you've got to have higher standards than  
6 just simply treating a side effect of the treatment  
7 and for a drug that may influence the cancer.

8 DR. NELSON: Larry Nelson. I voted no, but  
9 actually I was going to vote yes, right up until the  
10 last minute. And the reason I voted no is because I  
11 agree with Dr. Rosen's perspective of, yes, let's get  
12 some data that their bone density is declining and  
13 then initiate therapy, because as I read the question  
14 it talks about bone loss. It's not talking about  
15 treatment of osteoporosis or prevention of  
16 osteoporosis. It's talking about treatment or  
17 prevention of bone loss. So the bone loss can still  
18 be prevented under the treatment paradigm. So that's  
19 why I voted no for this.

20 DR. MARGOLIS: David Margolis. I voted no,  
21 really for the same reason. I think a fine treatment  
22 study was done, but we still need a fine prevention

1 study.

2 DR. BUZDAR: Buzdar. I voted no, because of  
3 concerns that it has not shown that it is safe to  
4 administer the antibody and that it has no adverse  
5 effect on the outcome of the disease.

6 DR. MORTIMER: Mortimer. No.

7 DR. RICHARDSON: Richardson. No. I think  
8 the safety concerns are real with this drug. The  
9 other aspect that I wanted to point out is the fact  
10 that when it comes to the issue of prevention, when  
11 you look at the use of a drug like zoledronic acid  
12 over the last several years in the medical oncology  
13 field, I think everybody has kind of revisited that  
14 particular drug with respect to schedule and how it's  
15 used. For some reason this got into the monthly types  
16 of regimens.

17 I think everybody has taken a second look at  
18 that and realized if you're really treating  
19 osteoporosis in these men, you treat them as though  
20 they have osteoporosis. That is once a year. I think  
21 there's a lot of stuff that is given out there for  
22 prevention, which rather than being preventive

1 medicine may be remunerative medicine.

2 DR. GULLEY: Gulley. I voted yes for the  
3 same reasons that Dr. Bennett and Dr. Carson already  
4 mentioned. Thanks.

5 MS. SOLONCHE: Solonche. I voted no.

6 DR. CARSON: Okay. Any other comments from  
7 the committee that need to be in the record?

8 Okay, well the committee voted against there  
9 being a favorable risk benefit ratio demonstrated for  
10 denosumab for the prevention of bone loss associated  
11 with hormonal ablation therapy in men with prostate  
12 cancer receiving androgen deprivation therapy. And  
13 the consensus of the committee was that there was not  
14 evidence as to the drug's safety in patients with  
15 prostate cancer and that this possible risk did not  
16 justify the issue of not being able to precisely  
17 choose in which patients this drug would prevent bone  
18 loss.

19 Okay. Well our session is over and again,  
20 this -- oh, I guess not. Sorry, I guess I'm hungry,  
21 right? I missed a total page. Okay.

22 Prior to the approval of an indication for

1 treatment or prevention of bone loss in patients with  
2 cancer, receiving hormone ablation, should data from  
3 studies designed to evaluate the effects of denosumab  
4 on skeletal related events, bone metastasis, in  
5 advanced cancers be required to be submitted to the  
6 agency for review to determine if there are any  
7 detrimental effects on cancer outcomes. So we just  
8 vote.

9 DR. COLLINS: I don't know that those  
10 studies as they've been described to us and the cancer  
11 metastasis preventions -- were the doses going to be  
12 12 times the dose that's here? I think if we're  
13 worried about long-term bone effects from over  
14 suppression with this dose, at a dose 12 times this  
15 doses, you know, we're going to see a different set of  
16 problems. And I don't know that that study  
17 necessarily really informs this dose in this patient  
18 population, personally.

19 DR. CARSON: Other? Yes?

20 DR. BUZDAR: Yes. I think the  
21 question -- if I understand the question correctly,  
22 the thing is that in cancer patients giving the

1     antibody therapy, number one thing which the sponsor  
2     has to show is that it is safe. It does not have an  
3     adverse outcome on the clinical course of the illness  
4     which the patient is being treated. I think that  
5     should be a must. And it has to be in very clear way,  
6     and stuff has to be there before we go there.

7             DR. CARSON: Dr. Gulley?

8             DR. GULLEY: So yeah, I think that the only  
9     indication that we have voted for is the prostate  
10    cancer indication in which they've showed relatively,  
11    I think pretty persuasively, with their bone scan data  
12    and their PSA data and their overall survival that  
13    there is no difference in this rather large cohort of  
14    men. So I think that I would agree with Dr. Collins,  
15    that if we're waiting until a study comes in with 12  
16    times the dose, that may inform the -- that may not be  
17    the right study to inform the safety for this study.

18            DR. CARSON: Dr. Mortimer?

19            DR. MORTIMER: But then maybe I'm  
20    misinterpreting the question, but isn't the question  
21    just saying what when you're using supportive care  
22    therapies, you have to make sure it does not impact on

1 the underlying malignant disease process, and I mean  
2 that's the obvious.

3 DR. PAZDUR: Correct. Let me give you some  
4 clarity here to our general advice --

5 DR. CARSON: Thank you.

6 DR. PAZDUR: -- and what we have given to  
7 companies. We were not involved with design of these  
8 studies, okay, as far as the oncology office was. The  
9 issue -- and we have many of these agents, such as  
10 radioprotective agents, neuroprotective agents,  
11 cardioprotective agents, et cetera, that come to our  
12 office. And in general, we ask sponsors to usually  
13 have co-primary endpoints of an effect on the endpoint  
14 of interest, whether it be, in this case, bone  
15 mineralization and then a primary endpoint of a PFS,  
16 or survival, et cetera to make sure of that effect.

17 However, what we're looking at here  
18 obviously is a set of studies that have been  
19 completed. And what we want to know is, is there any  
20 detrimental effect. Again, these are not as good as a  
21 prospective evaluation of a time to event endpoint  
22 such as survival, progression free survival, but at

1    least it will give us a hint.  In the studies using a  
2    higher dose, if we do see an effect, then the question  
3    is somewhat answered.

4                I guess one of the questions that I want to  
5    pose, because I think most people would agree to this,  
6    is should there be separate studies that look  
7    prospectively at this endpoint before these drugs are  
8    approved for a cancer agent?  So could we change the  
9    question?  Because would most people probably agree  
10   with this?  I take from the discussions that people  
11   are interested in it.

12               DR. COLLINS:  I agree and, in fact, that was  
13   just the point that I was getting at, that the data  
14   from the metastasis study is going to be so different  
15   from this that it really --

16               DR. PAZDUR:  Okay.  So could I change the  
17   question to the following?

18               Should a decision on these products in  
19   oncology be deferred until new trials are designed  
20   that look at a primary endpoint of survival or  
21   progression free survival, some time to event  
22   endpoint, in conjunction with a endpoint of bone loss



1 or fracture prevention, some type of bone endpoint?

2 DR. CARSON: I think maybe that's why it was  
3 a Freudian slip that I missed that last page, but FDA  
4 does not like the questions changed. And there has  
5 also been a rather standing rule that we don't change  
6 the questions.

7 If I can get some feedback from FDA as to  
8 whether or not --

9 DR. PAZDUR: I am FDA, so --

10 DR. CARSON: Well I know that, but I just  
11 wondered if you were the most senior FDA person, okay?

12 DR. PAZDUR: Yes, I am the most senior  
13 person here, so I can change the question, because I  
14 wrote the first question.

15 DR. CARSON: Okay. So you were the one who  
16 wrote it. You were the one who wrote them? Okay. So  
17 you're changing it then and to -- go ahead.

18 DR. PAZDUR: Should there be new trials that  
19 are initiated that look at a co-primary endpoint that  
20 are cancer related, outcome related, i.e., progression  
21 free survival or survival?

22 DR. CARSON: And are you asking for this

1 specific drug rather than as a general rule regarding  
2 REMs.

3 DR. PAZDUR: Correct. Right.

4 DR. CARSON: Okay.

5 DR. COLLINS: This drug in this dose,  
6 correct?

7 DR. PAZDUR: What's that? Yes.

8 DR. MARGOLIS: And you want the data from  
9 that trial -- you're suggesting the data from that  
10 trial be available before --

11 DR. CARSON: Approval.

12 DR. PAZDUR: Correct.

13 MR. GOOZNER: Question.

14 Dr. Pazdur, isn't there a difference between  
15 testing a drug that makes sure that the cancer doesn't  
16 get worse, so it's a safety signal?

17 DR. PAZDUR: It's a safety signal.

18 MR. GOOZNER: As opposed to an improvement  
19 in the cancer which is a cancer drug.

20 DR. PAZDUR: I think that's a good point  
21 too; you know, the issue of a loss of having the drug  
22 available to these populations versus having

1 definitive proof here. And here again, I'm bringing  
2 this question up for discussion and a vote.

3 DR. CARSON: And could you just -- looking a  
4 little ahead -- now the new question, how does that  
5 differ from 6A?

6 DR. COLLINS: Well there's a problem here  
7 because the committee voted yes to 6A, but no to 6B  
8 and this -- or excuse me -- 4A and 4B, but then this  
9 question here is treatment or prevention lumped  
10 together. So we already said yea for treatment and  
11 nay for prevention, when now they're lumped here and  
12 so --

13 DR. CARSON: Well he's saying any approval  
14 before the drug is --

15 DR. COLLINS: We'll be contradicting  
16 ourselves to some -- some of us will be contradicting  
17 ourselves if we want to vote yes here.

18 DR. CARSON: No. All he's saying is prior  
19 to approval of any indication should -- right? Should  
20 there be additional studies to show that the drug  
21 doesn't have an effect on cancer?

22 DR. COLLINS: But if we voted yes to 4A,

1     then we should vote no to this.

2                 DR. MARGOLIS:   Well then what have we been  
3     doing for the last 45 minutes?

4                 DR. JOHNSON:   It also doesn't address the  
5     prostate versus breast cancer.   It says all.   Okay.

6                 DR. CARSON:    Dr. Nelson?

7                 DR. PAZDUR:    So you want to change another  
8     question.

9                 UNIDENTIFIED SPEAKER:   Well I suggest that  
10    we delete the question or we all vote abstain.

11                DR. PAZDUR:    Okay.   Why don't we go back to  
12    the original question then?   Okay.   Would people feel  
13    comfortable with just looking at the data from  
14    existing studies and making some conclusions?   We'll  
15    go back to the original question.

16                DR. CARSON:    I guess that rule stands.

17                DR. PAZDUR:    Okay.

18                DR. CARSON:    Okay.   So what the question is,  
19    is that prior to the approval of this drug for any  
20    approval, either treatment or prevention, should there  
21    be additional data or studies that are related  
22    specifically to the drug's effects on skeletal related

1 events in advanced cancer patients.

2 DR. MARGOLIS: Isn't that what we've been  
3 doing for the last 45 minutes and some people who  
4 voted no said they wanted more data? Some people  
5 voted yes, thought there was enough data. I mean how  
6 is that any -- I mean are we going to revisit the last  
7 45 minutes?

8 DR. CARSON: So the question is, do you want  
9 more data?

10 DR. MARGOLIS: But we already answered that.  
11 I mean some people said no, they wanted more data.  
12 Some people said yes, they thought the data was  
13 sufficient, that the risk profile was such that it  
14 should be used for treatment. I mean, that's what  
15 we've been talking about for about 45 minutes now.

16 DR. CARSON: Dr. Buzdar?

17 DR. BUZDAR: I think the thing-- which if I  
18 as an oncologist -- the first thing is in oncology you  
19 want to look at it, that what is anything you do has  
20 impact on the outcome of the disease, i.e., cancer.  
21 So I think that has to be the most important thing.  
22 An intervention altering one aspect of the disease,

1 but overall affecting adversely the disease process  
2 for which we are treating, is I think an adverse  
3 effect. I think it doesn't make any sense to approve  
4 that type of approach.

5 DR. CARSON: Dr. Nelson?

6 DR. NELSON: I hope we delete the question.

7 DR. PAZDUR: If people feel that we've  
8 already answered this question, then that's fine with  
9 us. Okay.

10 DR. CARSON: Okay, so --

11 DR. PAZDUR: We can move on.

12 DR. CARSON: The summary of the discussion  
13 here is that we have, in essence, given our advice to  
14 FDA and this question has in essence already been  
15 answered.

16 DR. PAZDUR: Okay.

17 DR. CARSON: Okay. Ms. Solonche?

18 MS. SOLONCHE: My reading of this question,  
19 it's talking about here the prevention of bone loss,  
20 whereas we have been talking in some cases about  
21 fracture. I think that's a major difference in this  
22 question. I don't see what's wrong with this

1 question.

2 DR. CARSON: I think what the question asks  
3 is, is there more data needed in both bone loss -- for  
4 approval for both bone loss prevention or fracture  
5 treatments. And the committee has in essence felt  
6 that there, in fact, was enough data present and we  
7 have in fact voted on that.

8 MS. SOLONCHE: Is this perhaps a question  
9 that is looking to the future, not at this particular  
10 treatment, and maybe that is something we should be  
11 concerned about, not at this meeting but at another  
12 time and a different place?

13 DR. PAZDUR: We already have stated policy  
14 in guidance that address this issue.

15 DR. CARSON: Okay. Let's move on to  
16 question 6A.

17 If approved, do you recommend that denosumab  
18 have a risk evaluation and mitigation strategy or  
19 REMs?

20 Is the committee familiar with REMs? It was  
21 mentioned in the first slides I think today.

22 Okay, shall we open up this for discussion?

1 Dr. Collins?

2 DR. COLLINS: Could someone from the FDA  
3 clarify for me exactly what a communication plan to  
4 disseminate information to healthcare providers is?  
5 What that looks like, how that is? An example perhaps  
6 of a drug that it's used for.

7 DR. BEITZ: Yeah, this is unlike a  
8 medication guide, which is information geared to  
9 patients in lay language. A communication plan would  
10 be something that the sponsor would undertake to  
11 disseminate information about the risks of the drug to  
12 prescribers and could include mailings of letters. It  
13 could include website information. It could include  
14 CME courses, that sort of thing.

15 DR. CARSON: Dr. Bennett?

16 I'm, sorry. Dr. Bennett?

17 DR. BENNETT: The company has already  
18 presented a post-marketing surveillance plan, and how  
19 is this different than we're asking from what the  
20 company already proposed that they're going to do?

21 DR. BEITZ: Okay. The pharmacovigilance  
22 plan would be designed to do risk assessment, to



1 identify signals. This has more to do -- the REMs, at  
2 least the medication guide and communication plan,  
3 have to do with communicating risk to persons, either  
4 patients or prescribers. It doesn't have to do  
5 anything with assessing risk.

6 DR. CARSON: Dr. Uzel?

7 DR. UZEL: I just wanted to give an example  
8 of the guidance that is distributed to the patients.  
9 Like when we prescribe quinolones like Levaquin to our  
10 patients, levofloxacin, the pharmacy when they're  
11 dispensing the medication, gives a little information  
12 thing that you are at risk of tendon rupture. So I  
13 guess this is an example of what a communication plan  
14 is that would be disseminated to the patients, right?

15 DR. BEITZ: A medication guide would be  
16 given to patients, and it's an FDA reviewed paper.  
17 It's a piece of paper that lists the risks that are in  
18 the package insert that professionals see, but it's  
19 written in lay terms. And that's given to the  
20 patients at the time that the patients generally  
21 either pick up a prescription or are dispensed the  
22 medication in the doctor's office. The communication

1 plan is geared to doctors and healthcare providers.

2 DR. CARSON: Dr. Nelson?

3 DR. NELSON: Would it be appropriate to get  
4 some information from the sponsor about their opinion  
5 about this?

6 DR. CARSON: No, actually we just want  
7 the -- FDA would just like to have the committee's  
8 opinion. They will solicit the opinion of the sponsor  
9 separately.

10 Dr. Buzdar?

11 DR. BUZDAR: Yes, I think the thing is that  
12 it is important to -- more education does not hurt  
13 anybody. I think if there is more information which  
14 is disseminated to the healthcare provider and to the  
15 consumer, I think it is always good. I would support  
16 that.

17 DR. CARSON: Okay. Any other comments  
18 before we vote?

19 Okay. So if approved, do you recommend that  
20 denosumab have a risk evaluation and mitigation  
21 strategy? There are 12 of the committee members who  
22 voted yes and one voted no. So let's go around and

1 see.

2 MS. SOLONCHE: Martha Solonche. I voted  
3 yes.

4 DR. GULLEY: James Gulley. I voted yes. I  
5 think that when there's a potential for a safety  
6 signal, I think it's important to have informed  
7 consent for the patients and for the physicians  
8 treating, and I think this may help.

9 DR. RICHARDSON: Ron Richardson. I voted  
10 yes.

11 DR. BUZDAR: Buzdar. I voted yes.

12 DR. MARGOLIS: David Margolis. I voted yes.

13 DR. NELSON: Larry Nelson. I voted yes.

14 And in fact, we should have a risk reduction and  
15 evaluation and mitigation strategy for everybody in  
16 this country.

17 MR. GOOZNER: I voted yes, and I would just  
18 add that I think it's especially important to have  
19 these kinds of strategies when you have a first in  
20 class drug.

21 DR. JOHNSON: Julia Johnson. I voted yes.

22 DR. CARSON: I voted no, because I don't

1 know that there is evidence to say that REMs actually  
2 is very helpful and just not costly.

3 DR. BENNETT: John Bennett. I voted yes,  
4 but I am concerned about the drain on healthcare  
5 dollars and physicians in healthcare deliverers' time.  
6 It's not clear to me whether it's going to be -- this  
7 bang is going to be worth the buck.

8 DR. UZEL: Gulbu Uzel. I voted yes as well,  
9 and I agree with Dr. Bennett regarding the concerns  
10 about the time and money we will spend on this.

11 DR. ROSEN: I voted yes. I think it's  
12 extremely important to clarify to practitioners what  
13 they're dealing with, especially first in class drugs.

14 DR. COLLINS: Collins. I voted yes for  
15 reasons previously stated.

16 DR. CARSON: The committee voted  
17 overwhelming in favor of a REMs strategy, and the  
18 consensus is that any educational piece to inform  
19 practitioners of the facts about especially this new  
20 class of drugs would be beneficial. So let's move to  
21 the last question.

22 If so, which elements should be included in

1 the REMs? A medication guide to inform patients about  
2 the risk of the drugs? A communication plan to  
3 disseminate information to healthcare providers? And  
4 any other issues. Let me open the discussion.

5 DR. BUZDAR: Number 3 should have been both.

6 DR. COLLINS: Yeah, it -- do we have -- can  
7 we choose one or the other?

8 DR. BUZDAR: I think we should change that  
9 to both. Third choice should be both.

10 DR. CARSON: Dr. Margolis?

11 DR. MARGOLIS: I agree. I think with a  
12 first in class drug, we're -- whether people voted yes  
13 or no, there's always been concerns about safety, that  
14 those safety risks need to be well communicated to  
15 both patients and providers.

16 DR. CARSON: Any other issues?

17 MR. GOOZNER: Yeah, this is all in the realm  
18 of hypothetical but it was triggered by comments from  
19 some of the physicians on the panel about the cost of  
20 this. I mean I don't know where we're going to be in  
21 five years or so, but it strikes me, as a person who  
22 works in a different industry and profession, that the

1    idea that we're going to have a doctor giving a shot  
2    in an office and we can't record who got it and what  
3    happened to that person, and then get that back to the  
4    Food and Drug Administration over time in a reasonable  
5    fashion, it strikes me as like \$1.38 in today's  
6    electronic environment, except if you don't have an  
7    electronic environment.

8                   And so I think that we ought to talk about  
9    the real costs of having a real risk mitigation  
10   strategy. I don't know that this is the right drug to  
11   have a registry for, but it certainly seems to be the  
12   kind of drug that you could easily have a registry  
13   for, because it is going to be administered in a  
14   physician's office.

15                  DR. CARSON: Dr. Johnson?

16                  DR. JOHNSON: Yes, I support that concept.  
17   I really do think this is so new and unique, and I  
18   think a lot of the things we said today reflected our  
19   concerns about the use of this medication, even though  
20   we do see the value and the studies were well  
21   designed, it really is important to get back the  
22   information on the potential long-term effects.

1 DR. CARSON: Other comments? Dr. Nelson?

2 DR. NELSON: I also like the idea of a  
3 registry.

4 DR. CARSON: Dr. Uzel?

5 DR. UZEL: I want to comment on if a  
6 physician feels, himself or herself, qualified to give  
7 this medication in his office. This is for the  
8 consumer advocates. The physician, you would assume,  
9 would be well communicated and knowledgeable about the  
10 risks and benefits of this medication. I just want to  
11 highlight the misbelief or distrust in the medical  
12 field. So I just want to assure you, and that's why  
13 everybody does what they do.

14 MR. GOOZNER: If I may respond. It's not  
15 out of distrust. It's -- one of the things -- I mean  
16 I've sat on a number of FDA advisory committees, and  
17 one of the things that we see over and over again is a  
18 lack of data about outcomes.

19 When we talk about risk evaluation,  
20 mitigation strategies, which were really a fairly new  
21 I think to the FDA -- and I think that they are  
22 struggling with how to do this. And I think that we

1 as advisors, that we should articulate that there is a  
2 new world coming, hopefully in medicine, in which we  
3 can gather a lot more information, a lot more easily  
4 about the use of drugs. And that as thought leaders,  
5 hopefully, that we should articulate that vision here.

6           So it's not a question about -- what  
7 physicians have done in the past shouldn't be what  
8 physicians aren't going to do in the future.

9           DR. CARSON: Any other questions before we  
10 go on to question number 7? Just teasing. That was  
11 preventing people from leaving the room.

12           The committee had suggested in their  
13 consensus to go forth and recommend a REM strategy,  
14 that perhaps a registry be one of these strategies as  
15 well as a patient information guide and a  
16 communication plan for disseminating information to  
17 healthcare practitioners.

18           Now the real end of the meeting is -- thank  
19 you, again, for all of your participation. I've  
20 certainly enjoyed spending this day with all of you  
21 and have learned a lot. Hopefully, you all agree with  
22 that. Thank you again. Bye.



1                   [Whereupon, at 4:59 p.m., the meeting was  
2   adjourned.]  
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