Trends-in-Medicine

August 2009
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Quick Pulse

Trends-in-Medicine
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FDA Advisory Committee Recommends Approval of Amgen's Osteoporosis Drug but has Safety Concerns

Gaithersburg, MD
August 13, 2009

The FDA's Reproductive Health Drugs Advisory Committee (RHDAC) recommended approval of Amgen's Prolia (denosumab) as a twice-a-year subcutaneous injection for the treatment of osteoporosis in postmenopausal women as well as for the treatment of bone loss in some patients undergoing hormone ablation therapy for prostate cancer who are losing bone mass. The panel determined that the drug is effective at increasing bone mineral density (BMD) and reducing the risk of fractures but did not recommend approval for four of the six proposed indications because of the potential for serious side effects and new tumors.

The votes were:

- YES on ***treating*** bone loss in **postmenopausal women with osteoporosis** – **Unanimously Yes**
- NO on ***prevention*** of bone loss in **postmenopausal women with osteoporosis** – **12 No, 3 Yes**
- YES on ***treating*** bone loss in **men with prostate cancer** on hormone ablation therapy – **9 Yes, 4 No, 1 Abstention**
- NO on ***prevention*** of bone loss in **men with prostate cancer** on hormone ablation therapy – **11 No, 3 Yes**
- NO on ***treating*** bone loss in **women with breast cancer** – **13 No, 2 Yes**
- NO on ***prevention*** of bone loss in **women with breast cancer** – **14 No, 1 Abstention**

The panel also voted 12-1 that the FDA should require a risk evaluation and mitigation strategy (REMS), although not without some comments that REMS are expensive and a waste of money. The panel also tabled a vote on whether Amgen should be required to provide data evaluating the effects of denosumab on skeletal-related events in advanced cancers.

The advisory committee was a sometimes uninformed panel, led by a largely clueless panel chair, Dr. Sandra Carson, professor of obstetrics and gynecology at Brown University's Warren Alpert Medical School and director of the division of reproductive medicine and infertility at Women and Infants Hospital of Rhode Island. Dr. Carson had a difficult time even pronouncing the word denosumab. When it came time to voting on the six key questions, she tried to end the session before the questions were finished because she, apparently, didn't realize there was a second page of questions.

Then, when Dr. John Jenkins, director of the FDA's Office of New Drugs in the Center for Drug Evaluation and Research (CDER), told Dr. Carson that he wanted to rewrite a question, she, not knowing who he was, asked if there was a senior FDA official who could authorize the change. Dr. Jenkins answered, "I am the senior official here. I wrote the question."

Some panel members also appeared not to know what a REMS is, and several did not think that a REMS was warranted, citing the ***expense***. The panel also divided itself between oncologists, such as Dr. Aman Buzdar of MD Anderson Cancer Center who was "not interested in skin infections," and doctors who had serious problems with denosumab's side effects.

BACKGROUND

Denosumab, a monoclonal antibody, is the first therapeutic RANK Ligand (RANKL) inhibitor. RANKL is an essential regulator of osteoclasts, the cells which break down bone. It plays a pivotal role in dendritic cell maturation and in B-cell and T-cell differentiation. It is a member of the tumor necrosis factor (TNF) family – which includes Amgen's Enbrel (etanercept), Johnson & Johnson's Remicade (infliximab), Abbott's Humira (adalimumab), and others. TNF plays a role in regulating the immune system and hematopoiesis. TNF gene mutations have been implicated in common variable immunodeficiency (CVID). The adverse effects of TNF-blockade include serious infection, early and delayed hypersensitivity reactions, lupus-like syndrome, demyelinating disease, and exacerbation of congestive heart failure (CHF).

Since 1992, 27 monoclonal antibodies have been approved for conditions ranging from organ rejection to cancer and autoimmune disorders. Some of these antibodies have had serious safety problems, including serious infections, anaphylaxis, and malignancies. Twenty of the 27 now have black box warnings, and some have required a REMS, both pre- and post-marketing.

Denosumab is being investigated for its potential to inhibit all stages of osteoclast activity through a targeted mechanism. It is the first type of drug in its class and acts differently than other osteoporosis drugs, such as Roche/GlaxoSmithKline's Boniva (ibandronate), Merck's Fosamax (alendronate), and Novartis's Zometa (zoledronic acid). The FDA is expected to decide whether to approve denosumab by October 19, 2009.

Amgen's studies included more than 7,800 postmenopausal women with osteoporosis and nearly 1,500 men with prostate cancer. Overall, the studies showed that the drug is effective. Two of the studies with fracture endpoints showed that denosumab reduced the incidence of fractures, and all six studies showed that the drug increased bone mineral density at all skeletal sites measured. A third study, although positive, had less impressive results. In that study, denosumab met its primary endpoint; patients on denosumab had a similar time to first skeletal-related event (SRE) compared to patients on IV Zometa in the treatment of bone metastases, but the delay in the time to first SRE was not statistically superior vs. Zometa.

THE FDA PERSPECTIVE

Efficacy

The FDA found that denosumab worked well in three major Phase III studies, significantly decreasing the risk of new vertebral fracture compared to placebo. Reviewers also agreed that it increased BMD in the lumbar spine and hips compared to placebo.

- **Study 20030216 (Postmenopausal osteoporosis – or PMO – fracture):** Statistically significant improvement in reduction of the incidence of new vertebral structure compared to placebo at Month 36 – a 68% decrease in the risk of new vertebral fractures.
- **Study 20040132 (PMO prevention):** Statistically significant increase in lumbar spine BMD at Month 24 compared to placebo. The overall treatment difference was +7%.
- **Study 20040135 (Hormone ablation – breast cancer):** Significant increase in BMD at Month 12 vs. placebo. The overall treatment difference was +5.5%.
- **Study 20040138 (Hormone ablation – prostate cancer):** Significant increase in BMD at Month 24 vs. placebo. The overall treatment difference was +6.7%.

Dr. Vaishali Popat, a medical officer in the FDA's Division of Reproductive and Urologic Products (DRUP), found that:

- Denosumab 60 mg every six months was effective in decreasing the incidence of fractures in postmenopausal women.
- The incidence of hip fracture was lower in placebo in the first and second year but was similar to placebo in the third year of the primary fracture trial.
- Treatment with denosumab resulted in an increase in BMD.
- There is profound suppression in markers of bone resorption.
- Once treatment is discontinued, BMD quickly returns to baseline.

Safety

FDA reviewers concluded that:

- Adverse events of greatest concern are:
  - New malignancies.
  - Tumor progression.
  - Dermatological adverse events.
- Deaths were not higher with denosumab therapy.

- There is an imbalance in serious adverse events with denosumab use.

FDA reviewers had many concerns about the safety of denosumab. The reviewers said that it "has the potential to affect multiple layers of the immune system which could result in the development of serious infections and cancer… (and patients on denosumab) had a slightly increased incidence of serious infections. There were more serious infections of the skin, ear, abdominal system, and urinary tract …(The) increased risk of serious skin infections…is important to the overall benefit:risk assessment…Also, endocarditis, infective arthritis, and skin ulcers occurred more commonly in denosumab subjects. There were three denosumab subjects in Phase I studies who developed pneumonia requiring hospitalization following a single dose of denosumab…Of particular concern, in light of these safety issues, is whether the risk:benefit balance for the osteoporosis prevention indication, both for patients with and without cancer, supports approval."

Adrienne Rothstein, PharmD, DRUP, gave the safety analysis of four trials. She summarized that there was an imbalance in the number of serious infections in the denosumab patients compared to placebo. She noted that new malignancies were also a reason for concern, and breast cancer was "a common adverse event." There were more events of neoplasm in the denosumab group compared to placebo. She said, "In primary PMO studies there were imbalances in malignancies in the denosumab group driven by cancers…the significance of these findings is unclear." As for dermatologic adverse events, she said that there was a statistically significant difference between treatment groups in dermatitis, eczema, and rashes.

Safety concerns include:

- **Infection:** Patients on denosumab had slightly increased incidence of serious infections.
- **Malignancy:** No carcinogenicity studies were performed. Overall, patients taking denosumab had a slightly increased incidence of several cancers.
- **Osteonecrosis of the jaw (ONJ):** No cases were positively adjudicated in the trials, but at least one confirmed case has been reported in another Amgen trial.
- **Bone biopsy histomorphometry:** The study results raised concerns about the degree of bone remodeling suppression. Patients on denosumab had markedly suppressed osteoclast and osteoblast counts compared to placebo and alendronate. Dynamic bone formation parameters such as activation frequency, bone formation rate, and mineralizing surface were also markedly suppressed. With long-term use, suppression of bone remodeling may lead to complications such as delayed fracture healing, ONJ, or atypical fracture.
- **Hypocalcemia:** Amgen proposed that this known class effect of antiresorptive drugs be a contraindication.
- **Skin and soft tissue disorder:** Denosumab patients were more likely to develop skin and soft tissue related adverse events, which were statistically significant.

Deaths and cardiovascular safety

The FDA reviewers did not find any red flags in the studies with regard to deaths and cardiovascular (CV) safety. There were 354 deaths in the denosumab trials: 169 in subjects with low bone mass or osteoporosis and 185 in patients with underlying cancer. The number of patients who died during the PMO fracture trial (216) was not higher with denosumab vs. placebo groups. There were no deaths in the PMO prevention trial (132). Serious adverse events were slightly higher with denosumab vs. placebo. The number of patients who died during the key hormone ablation studies was not higher with denosumab compared to placebo (45 vs. 47). The FDA reviewers found no differences between the two groups with regard to cardiovascular adverse events.

The FDA reviewers noted that the postmenopausal population who might use denosumab for several years is a high-risk population for CV disease, and a concern was raised for the potential for denosumab to cause atherosclerosis. This was based on reports in the published literature regarding a possible association between osteoprotegerin (OPG) levels and arterial wall calcification, cardiovascular disease, and mortality, and the possibility that inactivation of RANKL by denosumab could result in elevated levels of OPG via an unopposed feedback mechanism.

Amgen established a committee to adjudicate possible CV events in two Phase III trials – one in postmenopausal women and one in men.

There was no clear increase in osteoprotegerin levels in patients taking denosumab compared to placebo. Adjudicated serious cardiovascular events were similar between the two treatment groups. No differences were found in aortic calcification scores at three years between the arms. However, the FDA reviewers said that lateral lumbar spine x-rays may not be a sensitive method to find small differences.

Adjudicated CV-Related Serious Adverse Events

Incidence at 36 months	Trial 216		Trial 138	
	Denosumab n=3,886	Placebo n=3,876	Denosumab n=731	Placebo n=725
Any adjudicated postive CV serious adverse event	4.8%	4.6%	10.9%	11%
CV death	0.6%	0.8%	2.6%	2.9%
Stroke/transient ischemic attack	1.4%	1.4%	2.9%	2.3%
Acute coronary syndrome	1.2%	1.0%	2.5%	3.7%
Congestive heart failure	0.7%	0.6%	1.1%	1.5%
Other vascular event	0.8%	0.8%	2.5%	1.7%
Arrhythmia	1.3%	1.2%	2.6%	2.1%

Infection

Patients taking denosumab had a slightly increased incidence of serious infections. There were more serious infections of the skin, ear, abdominal system, and urinary tract. Endocarditis, infective arthritis, and skin ulcers occurred more often in patients taking denosumab. There were four cases of endocarditis in the denosumab group. Three denosumab patients in Phase I studies developed pneumonia requiring hospitalization following a single dose.

The FDA reviewers said that the target population for osteoporosis treatment or prevention is postmenopausal women who might use the drug for many years, and who might have impaired immune systems, comorbid conditions, or concomitant medications. The reviewers wrote, "It is biologically plausible that (denosumab) could increase the risk of infection."

The overall incidence of serious adverse events of infection in the primary PMO studies was higher with denosumab than placebo (4.4% vs. 3.5%). Infections related to bacteria and unspecified pathogens occurred more often in denosumab patients. Serious bacterial infections occurred more often with denosumab (0.7% vs. 0.4% with placebo), and serious infections due to an unspecified pathogen were higher with denosumab (3.7% vs. 3.1%).

Primary Infection Concerns

Measurement	Denosumab	Placebo
Pneumonia in Phase I studies following a single dose of denosumab	3 hospitalized	---
Endocarditis	4 cases	---
Serious abdominal and gastrointestinal infections	0.8%	0.6%
Serious urinary tract infections	0.8%	0.5%
Infective arthritis	0.1%	0
Ear infections	0.1%	0
Serious skin infections		
Streptococcal	0.2%	0.03%
Bacterial	0.3%	0.1%

Adverse Events of Concern in the Neoplasms System Organ Class (SOC) in Primary PMO Studies (*pooled data*)

High level group term	Denosumab	Placebo
Any event in the neoplasms SOC	8.4%	7.7%
Any event of malignancy or unspecified neoplasm	5.6%	4.9%
Specific neoplasms		
Breast – benign (*including nipple*)	5.4%	4.8%
Breast – malignant and unspecified (*including nipple*)	11%	10.4%
Endocrine – malignant and unspecified	2.2%	0.7%
Pancreatic – malignant *(excluding islet cell and carcinoid)*	2.5%	1%
Gastrointestinal – malignant and unspecified	11%	8.3%
Colonic – malignant	3.8%	2.8%
Gastric – malignant	2.2%	1%
Reproductive – female malignant and unspecified	6.6%	3.1%
Ovarian – malignant *(excluding germ cell)*	3.1%	1.7%
Uterine – malignant	1.3%	0.4%

Malignancy

Several malignancies occurred at a higher incidence in denosumab patients. Overall, denosumab patients in the primary PMO safety population had a slightly increased incidence of breast cancer, pancreatic cancer, gastrointestinal cancer, and reproductive cancers. **FDA reviewers said, "This finding of an increased incidence of certain gastrointestinal, reproductive, and endocrine malignancies is important to the benefit:risk assessment for this product, particularly for the osteoporosis prevention indication."**

Breast cancer was the most common adverse event that led to discontinuation of the drug in the primary PMO safety population; discontinuations because of breast cancer were higher with denosumab than placebo (0.5% vs. 0.3%).

FDA reviewers said that Amgen did not perform the usual carcinogenicity studies in animals because denosumab is not active in normal mice or rats. However, the data showed an increase in some malignancies in humans. The reviewers noted, "Three subjects receiving a high dose (100 mg)…in a dose-finding study (223) died of a new malignancy." The 60 mg dose was used in the Phase III studies.

The reviewers said that the incidence of malignant female reproductive neoplasms with denosumab was two-fold higher compared to placebo (21 vs. 9 patients). Malignant gastrointestinal neoplasms were also reported more frequently in denosumab subjects (35 vs. 24), and malignant breast neoplasms were slightly more frequent in denosumab patients (35 vs. 30). Although not commonly reported, malignant endocrine neoplasms were reported for denosumab at a three-fold higher rate compared to placebo. Three denosumab patients developed hematopoietic neoplasms compared to none in the placebo group. The only malignancy that occurred more often in the placebo group was malignant respiratory neoplasms (15 vs. 24).

The FDA requires that supportive care oncology drug and biologic products given to cancer patients that either (1) inhibit the anticancer action of the drugs, or (2) enhance neoplastic progression by acting as growth factors, be carefully evaluated in studies to identify any detrimental effects on progression free survival (PFS) or overall survival (OS). However, the denosumab trials did not contain "pre-specified, defined, rigorous plans to evaluate for potential treatment effects on time-to-disease progression. There were no specific instructions in either Trial 135 or Trial 138 related to assessment of these trials. In both trials, OS was a designated exploratory endpoint, but neither trial was designed to detect a clinically meaningful decrement in overall survival. An OS analysis in Trial 135 was not performed because there was only one death in each arm. Trial 138 did an analysis of OS, and there was no difference in overall survival between denosumab and placebo.

Osteonecrosis of the jaw (ONJ)

Osteonecrosis, or avascular necrosis, of the jaw is a pathological process associated with pain, swelling, exposed bone, local infection, and pathologic fracture of the jaw. The FDA reviewers said, "Post-marketing experience with bisphosphonates has raised concerns about the potential for bone remodeling inhibition and osteonecrosis of the jaw. Risk factors for bisphosphonate-associated ONJ include long-term use (≥3 years), patients with malignancy, poor oral hygiene, dental procedures, concomitant therapies such as radiation, chemotherapy, corticosteroids, and IV use of bisphosphonates. The mechanism by which osteonecrosis develops in relationship to treatment with bisphosphonates is not well understood…The true incidence and risk of ONJ related to treatment with denosumab is unknown; however, based on its antiresorptive effects, there is a recognized risk that patients treated with denosumab have the potential to develop ONJ."

Amgen formed an adjudication committee to review 21 identified potential cases of ONJ. The committee concluded that none was positive for meeting the *company's* definition of ONJ. The FDA requested more information from Amgen, and agency experts agreed with Amgen's committee. The reviewers said, "It should be noted that while no cases of ONJ have been confirmed in the PMO and hormone ablation trials under review, at least one confirmed case of ONJ has been reported in other trials conducted (by Amgen) in patients with multiple myeloma and metastatic cancer."

Bone Histomorphometry

Dr. Theresa Kehoe, clinical team leader, DRUP, said that the FDA is concerned about overall bone turnover and bone resorption with denosumab:

- Treatment with denosumab decreases bone resorption.
- Bone resorption and bone formation are tightly coupled processes.
- Treatment with denosumab also decreases bone formation or overall bone turnover.

The FDA reviewers said that the bone histomorphometry results "raise concerns regarding the degree of apparent bone turnover suppression and the potential for long-term safety consequences." Markers of bone dynamics including activation frequency, mineralizing surface, and bone formation rates were lower in denosumab patients compared to patients on alendronate. Osteoclasts and osteoblasts were suppressed relative to patients taking placebo and alendronate. The reviewers said that they are worried that with long-term use "suppression of bone remodeling may lead to complications such as delayed fracture healing, osteonecrosis of the jaw, or atypical fracture."

Two ***New England Journal of Medicine*** articles published in mid-August 2009 did not find any signs of delayed bone healing after fracture.

The presence of double tetracycline labeling in a biopsy specimen indicates active bone remodeling and formation. The usual evaluation site is trabecular bone, the most active site of bone remodeling. All patients on placebo had double label present, but 21% of denosumab patients had no tetracycline label present at 12 months. No label was present at either 24 months or 36 months in 35%. The FDA reviewers wrote, "While a sporadic biopsy specimen with absence of double label is not unusual, the number of patients treated with denosumab who have absence of double labeling is striking. The clinical consequences of these findings are unclear. One concern is that absence of a double label may suggest over suppression of dynamic bone formation parameters."

The FDA reviewers looked at Study 234, which had data on bone histomorphometry in patients previously on alendronate who either continued that therapy or were switched to denosumab, "This study offers important safety information for patients who may be switched from bisphosphonate to denosumab." In the study, activation frequency was further suppressed with initiation of denosumab treatment compared to alendronate therapy. Bone formation rate increased with denosumab compared to continued alendronate therapy. Eroded surfaces decreased substantially with denosumab. Osteoid surfaces were further decreased with denosumab, "suggesting decreased remodeling." Mineralization lag time and osteoid thickness were not appreciably changed with denosumab compared to alendronate. Osteoid volume was further decreased with denosumab, "again suggesting that bone remodeling is further decreased" with denosumab.

The FDA reviewers summarized that denosumab "significantly reduces bone remodeling. However, the number of biopsy specimens that lacked any tetracycline label or sufficient label to allow appropriate dynamic analyses is of concern. While it is common to have a small number of biopsy specimens that lack tetracycline labeling, the numbers seen in these…trials have not been encountered before… Overall, there is significant concern regarding over suppression of bone turnover. However, the clinical consequences of these bone histomorphometry findings are not clear…The long-term risks of adverse effects related to severely suppressed bone turnover may not be fully recognized."

Hypocalcemia

The FDA reviewers found that denosumab decreases bone resorption, which plays an important role in calcium homeostasis, "It is physiologically plausible that denosumab administration and associated suppressed bone remodeling may lead to higher incidence of hypocalcemia…Denosumab-induced hypocalcemia appears to be transient (in first month after dosing, nadir at day 8-11) with spontaneous resolution without any serious sequelae observed in this study."

Dermatologic adverse events (excluding infections)

Patients on denosumab were more likely to develop skin and soft tissue related adverse events: 16% of denosumab patients had adverse events related to skin and soft tissue disorders vs. 13% with placebo.

Epidermal and Dermal Conditions

Adverse event high level term	Denosumab n=3,765	Placebo n=3,769
Total subjects with epidermal and dermal conditions	450	343
Bullous conditions	9	3
Dermal and epidermal conditions	69	56
Dermatitis and eczema	148	83
Dermatitis ascribed to specific agent	6	1
Photosensitivity conditions	6	1
Pruritus	112	97
Rashes, eruptions, and exanthems	116	91

Pancreatitis

Pooled data using the narrow SMQ (standardized medDRA queries) for acute pancreatitis yielded nine events in eight patients taking denosumab and four events in four patients on placebo. There were more serious events of pancreatitis in the denosumab group. Two denosumab patients developed pancreatitis that resulted in death.

Eight patients on denosumab developed pancreatitis in the primary PMO studies. One case "was concerning for a potential causal relationship – a subject with no known risk factors and who had been taking denosumab for more than two years developed pancreatitis less than three weeks after receiving a dose. Some of the remaining cases were confounded [prior history of pancreatitis – three subjects, hypercholesterolemia (unknown triglyceride levels) – one subject]. One patient died about four months after receiving the first dose of denosumab, but the family refused to provide information."

Hypersensitivity and immunogenicity

Incidences of hypersensitivity and drug hypersensitivity were 0.7% and 0.4%, respectively in the denosumab group and 0.6% and 0.3% in the placebo group in the primary PMO and primary hormone ablation safety analysis sets.

Risk:benefit summary assessment

Dr. Kehoe talked about the FDA's interpretation of the populations of patients for whom the indications are intended. She said that for treatment of PMO, the indication encompasses all patients with osteoporosis diagnosed by BMD or history of low trauma fracture. She said that the FDA didn't include the FRAX calculator (a fracture risk assessment tool used by Amgen), but "We do believe that the treatment of PMO indication also encompasses patients at increased risk for fracture based on the FRAX calculator. This would include patients with low bone mass not considered at increased risk of fracture based on the FRAX calculator."

As for treatment of bone loss for patients undergoing hormone ablation, Dr. Kehoe said that the indication would include patients who have evidence of osteoporosis as well as those on hormone ablation therapy and demonstrating significant bone loss. This includes patients with normal BMD or normal BMD who don't have significant loss with hormone ablation therapy or have newly begun hormone ablation therapy.

Regarding treatment guidelines, Dr. Kehoe said, "The agency's interpretation aligns with the currently published treatment guidelines for postmenopausal osteoporosis. It recommends BMD testing for women over the age of 50, initiation of therapy for history of fracture, T-score less than 2.5, or increased 10 year fracture risk based on FRAX. ASCO also recommends BMD testing to all women on aromatase inhibitors and initiation of therapy for those with a T-score less than 2.5. There are no current guidelines for prostate cancer patients.

Dr. Kehoe said that denosumab is effective for an increase BMD in:

- Postmenopausal women with low bone mass.
- Women undergoing aromatase inhibition therapy for breast cancer.
- Men undergoing androgen therapy for prostate cancer.

She added that neither of the primary trials evaluating the drug in hormone ablation populations contained pre-specified plans to identify detrimental effects on cancer outcomes using PFS or OS. OS was an exploratory endpoint in both cancer trials; however, given the eligible population for enrollment, few events would be anticipated.

FDA safety concerns remaining include:

- Imbalance in infection serious adverse events, most notably of the skin, ear, and urinary tract.
- Imbalance of endocarditis (while low, it did exceed what was expected).
- Imbalance of infective arthritis.
- Imbalance of new malignancies.
- Imbalance of tumor metastases.
- Imbalance of dermatologic adverse events.

Dr. Kehoe said, "The question of over-suppression of bone turnover remains…In the program we had discovered significant suppression of the marker CTX (carboxy-terminal collagen crosslinks). The bone formation marker is also significantly suppressed. When combined, **the concern remains for the potential for long-term consequences of this degree of suppression of bone formation and turnover. It is not possible to predict long-term outcomes based on the data that we have; we can only say that they are unclear**." She reiterated the FDA's concern about hip fractures in the long term.

AMGEN'S PERSPECTIVE

Amgen told the panel that denosumab meets an unmet need and offers a "meaningful alternative to existing therapies" for postmenopausal osteoporosis patients and for prostate and breast cancer patients. Amgen senior vice president Dr. Paul Eisenberg said, "The overall safety profile compares to other therapies in efficacy and in some cases appears superior. There is an unmet need in both populations, and denosumab shows efficacy in preventing bone loss and fractures."

Dr. Ethel Siris, an endocrinologist from Columbia Medical Center and New York Presbyterian Hospital, speaking for Amgen, said that "one size does not fit all" when it comes to therapies for postmenopausal women with low bone mass or osteoporosis. Problems with current therapies include GI tolerance, side effects, renal issues, and different efficacy profiles. There are also no approved therapies for bone loss in breast and prostate cancer patients on hormone ablation therapy. Dr. Siris commented, "When we see these patients we know they're losing bone, and we don't have an approved treatment for them. One of the biggest problems in our field is adherence. At least half of the patients put on an oral agent for osteoporosis are not on it after a year. Giving twice-yearly injections may be more convenient for the patient, and the doctor will know if the patient is taking the medicine."

Amgen senior vice president Dr. David Lacey said, "There is an important need for another option for the treatment of osteoporosis." He discussed the science of the drug, and said that RANKL inhibitors do not interfere with other therapies, including chemotherapy, targeted, and hormonal therapies. He said that RANKL inhibition reduced skeletal tumor progression in cancer models and did not interfere with anti-tumor therapies.

Dr. Catherine Stehman-Breen, vice president of global development for Amgen, talked about denosumab's clinical efficacy and safety assessments. She said that:

- Denosumab reduced the risk of new vertebral fracture.
- Denosumab significantly reduced the risk of hip fracture.
- Risk reduction was consistent over time and seen as early as one year.
- Reduction of non-vertebral fractures also was seen.
- Histomorphometry findings were consistent with reduced bone turnover.
- The level of suppression has caused concern, but it has not been associated with any adverse consequences such as abnormalities in fracture healing, atypical fractures, or ONJ.

Dr. Stehman-Breen said that denosumab resulted in increased BMD and noted that the effect of denosumab on serum CTX and on BMD is reversible. She said, "Clinical efficacy data have demonstrated significant and rapid reductions in bone resorption that have translated into robust increases in BMD and, most importantly, have demonstrated significant reductions in fracture risk at the spine, hip, and non-vertebral sites."

She said that overall adverse events in hormone ablation therapy were comparable to placebo (87% for placebo vs. 87.8% for denosumab). Serious adverse events occurred in 27.6% of patients on placebo and 31.6% of denosumab patients, "Withdrawals leading to discontinuation or stopping the drug were rare and balanced between the two groups. Death incidence was similar between the two groups."

Dr. Stehman-Breen described a number of pre-specified adverse events including hypocalcemia, non-union or delayed fracture healing, and infections. She said that symptomatic hypocalcemia "was rare and balanced between groups." As for non-union or delayed fracture healing, "These events were uncommon with three in each." With regard to infections, she asked, "Did denosumab have a clinical impact on the immune system? The overall adverse events of infection were the same frequency between the two groups. Serious adverse events of infection occurred in 3.4% of the placebo group and 4.3% receiving denosumab, a difference that was not statistically significant. Opportunistic infection adverse events were well balanced between patients on placebo and those on denosumab."

Infection

Dr. Stehman-Breen summarized:

- Overall adverse events of infection were balanced.
- No increased risk of opportunistic infections.
- Skin infections resulting in hospitalizations were observed more frequently in denosumab-treated patients (0.4% denosumab vs. 0.3% placebo).
- Current infections were infrequent.
- No increased risk of sepsis or death was observed in denosumab patients.

Malignancy

Dr. Stehman-Breen told the panel that malignant tumors were not greatly different from placebo. She noted the FDA highlighted three subjects who died of a new malignancy, explaining, "This is an understandable concern. This was a four-year study with 412 subjects with a mean age of 64. Seven-fold more women were randomized to receive denosumab than placebo, so this is not unexpected. The overall incidence of malignancies was well balanced between the subjects in each group."

Dr. Stehman-Breen noted:

- In preclinical studies, RANKL inhibition did not promote cancer development or progression.

- No statistical difference in overall incidence of malignancies in bone loss program.
- In PMO fracture study there was no increased risk of death due to neoplasms.

Target-specific safety considerations

Dr. Stehman-Breen pointed out that:

- Most adverse events associated with monoclonal antibodies are related to the therapeutic target.
- RANKL inhibition decreases bone turnover – no evidence of adverse events associated with reduction of bone turnover for up to five years.
- No evidence RANKL inhibition results in impaired immune function in adults from their preclinical or clinical studies.
- Inhibition of RANKL prevented tumor metastases to bone in preclinical models.

Dr. Eisenberg asked, "What about denosumab? What do we know about RANKL inhibition? The predominant effect…is the reduction in bone resorption with expected increases in BMD and bone strength. It will be important to ensure that there is long-term follow-up with patients treated with denosumab…There have been signs of increased signals of infection in these patients. What we know is that there doesn't appear to be an increased risk of viral infections. Overall, there are small differences in common bacterial infections but not with respect to severity, rate of sepsis, or rate of death…If it is a real signal, it is possible that there is a relation to a skin-specific response, such as increased inflammatory response. Since RANKL is expressed in skin immune cells, this may be an effect."

Dr. Eisenberg added, "There was no statistically significant difference in overall adverse events of malignancy. There was no increase in deaths related to malignancy, and overall rates in malignancy that we observed are within the range expected in the patient populations we studied. Finally…there was a potential for denosumab to prevent tumor metastases to bone and that is being studied…The expected effect of denosumab inhibition on RANKL is decreased bone absorption, and our data have suggested that there may be altered skin immune reactivity in some patients."

Risk:benefit

Dr. Stehman-Breen argued that:

- Denosumab has a favorable safety profile.
- Overall incidence of eczema observed more frequently in women with PMO, and cataracts were seen more frequently in men.
- Overall adverse events were mild to moderate in severity and well balanced between the two groups.
- Skin infections requiring hospitalization was slightly higher in the denosumab group.
- Denosumab did not demonstrate an increased risk of malignancy; however, we recognize that defining the safety profile is an ongoing process, and we have designed a comprehensive program which includes clinical trials and observational studies to further define the safety profile.

Amgen's Dr. Eisenberg said that denosumab's efficacy is supported by a strong pharmacovigilance program, which he described in detail. The program includes long-term follow-up studies, proactive safety surveillance, and clinical trials.

Dr. Eisenberg said that Amgen's vision of risk assessment continues throughout the life of the drug in the marketplace. The company plans to conduct placebo controlled trials and long-term follow-up of patients as well as do proactive safety surveillance. This includes extension studies of Phase II and III studies, and some patients will be followed up to 10 years. He added that there is an ongoing placebo-controlled study in Japan that will provide safety data. The PMO observational safety study design will include characterizing denosumab patients in clinical practice, assess rates of adverse events of interest, and detect rare events. It will use data from large healthcare data systems in the U.S. and Europe and will compare cancer rates to reference data, looking at >300,000 patients over five years.

Amgen's plan includes a new study of 2,800 patients of which 1,200 are enrolled, with the primary endpoint fracture prevention. The trial also has endpoints related to cancer occurrence.

Amgen also has designed a placebo-controlled study (to be completed in 2011) to examine the problem of cataracts in men with prostate cancer. An analysis of several studies in advanced cancer (breast, prostate, and solid tumors) is ongoing. Although it isn't completed, Dr. Eisenberg said that "from a safety perspective, overall survival (in the solid tumor study) was similar between the two groups." He added that higher doses of denosumab are being examined in a study of prevention of metastases in prostate cancer. That study is fully enrolled and will complete four years of follow-up next year. A breast cancer study will begin later this year and will provide data on tumor progression.

Dr. Eisenberg insisted that the safety issues "can be minimized through labeling." He said that labeling should contraindicate use in patients with hypocalcemia and should recommend calcium and vitamin D supplementation. Labeling would also advise patients to seek prompt medical attention at any signs or symptoms of skin eruptions.

PANEL QUESTIONS FOR AMGEN

The panel did not ask the FDA presenters any questions but asked Amgen a wide variety of questions.

Who gets treatment?

A panel member asked how to predict which patients should get denosumab and how early should treatment begin. Amgen's Dr. Stehman-Breen answered that the idea that osteopenia is a precursor to osteoporosis is an outmoded concept, "We now have a better way to identify those patients with a high risk of fracture instead of simply looking at BMD (including FRAX calculations)." Dr. Scott Emerson, a biostatistician from the University of Washington, asked, "We have two different indications – one is treatment, and we have 8,000 treatments – and the other is prevention, and we have 300 women treated under that…How early should we start treatment? And looking at risk factors...when does prevention start?" Dr. Siris said, "Osteopenia is a risk factor; it's not a disease. It's a lowness of BMD which can promote fracture risk…You (Dr. Kehoe) consider a high FRAX score a treatment indication. I'd say that would qualify for treatment under the treatment indication. Right now, third-party payers won't cover an osteopenic woman, and we're caught in a situation where we're going to have to redefine some things, to make sure women can get medication and get reimbursed."

Renal effects

Dr. Emerson, the biostatistician, asked if denosumab can be given safely to patients with abnormal renal function. Dr. Stehman-Breen answered that women in the fracture study were not excluded based on the level of renal function, and the efficacy of denosumab was "identical to that seen in the larger population." She added that the drug does not cause acute renal failure.

Drop-outs

Asked about the number of women who dropped out of the trials because they were diagnosed with breast cancer (a third of patients did so), Dr. Stehman-Breen said, "We had a similar rate of new breast cancers diagnosed in our large postmenopause osteoporosis study. What was different was the number of discontinuations due to adverse events of breast cancer."

A panel member asked why twice as many women taking denosumab as those taking placebo discontinued participating in the study due to a diagnosis of breast cancer. Dr. Stehman-Breen answered, "There didn't appear to be a pattern that suggests that these subjects were diagnosed earlier." An Amgen oncologist added, "The rates of new cancers are essentially the same (between the two groups). The reasons for discontinuations are not apparent. The types of cancers are similar, scattering over three years."

Immunosuppression and infection

Dr. Julia Johnson, a gynecologist from the University of Vermont, asked about immunosuppression and what appeared to be a fairly consistent finding of higher risk of infection in denosumab patients vs. placebo. Dr. Stehman-Breen said that the PMO fracture study has a large, open-label, single-arm, extension fracture study ongoing for a little over a year, but data are limited so far, "We haven't seen any unexpected infections such as an unexpected higher rate of opportunistic infections." She added that Amgen hasn't seen a higher risk of serious adverse events to date in the study.

A panel member asked about the huge percentage of skin infections in the lower extremities and wondered if they might be related to venous disease, if the patients received intravenous (IV) antibiotics, and if they had fever or high white counts. He also asked about hip fractures and a secondary analysis of Study 216 which showed that patients on denosumab had an equivalent number of hip fractures at three years vs. placebo. He asked how many patients who had hip fractures stayed in the trials. Dr. Stehman-Breen responded, "In patients who developed cellulitis and erysipelas (a superficial bacterial skin infection) the mean age was 79 in placebo and 84 in the denosumab group…The level of severity was generally similar between those in placebo and those in the denosumab group. There was one fatal adverse event of cellulitis in one subject who was quite complicated and had advanced pancreatic cancer that invaded into the ventricle. The vast majority were lower extremity infections – 100% in placebo and 88% in the denosumab group. Most were hospitalized, received IV antibiotics, but none discontinued the study. Not all had fevers or chills – 15% had fevers, 50% had pain, 50% swelling and erythema. These are often complicated patients, and diagnosis can be complex."

Hip fractures, bone mass density, and bone remodeling

Regarding hip fractures in Year 3 between denosumab and placebo, Dr. Stehman-Breen said, "Although they are very small numbers, it was slightly greater in those subjects treated with denosumab. One thing that is important to note is that the fracture rate in the placebo group – hip fracture – was declining in that last year, while in the denosumab group it was staying the same. It's possible that this may reflect the survivorship phenomenon." She added that some patients with hip fractures continued the studies, and some dropped out.

Dr. Clifford Rosen, an endocrinologist, senior staff scientist at the Maine Center for Osteoporosis, and a BMD researcher, asked about the relationship between the change in BMD that occurs in the first year after stopping treatment and what happens with estrogen withdrawal, "Is it the same slope of change or more rapid?...How does that relate to the increase in fracture numbers that we saw in the 132 study?" Dr. Stehman-Breen said that there were more fractures in patients treated with denosumab during the off-treatment period, but added, "When looking at osteoporotic fractures, the fractures

were similar…We did a post hoc analysis and looked at those subjects in the PMO fracture study who discontinued therapy but continued participating in the study. When we looked at those fracture rates, we looked at patients who had as much as seven months follow-up. Fracture rates per 100 years were similar compared to those treated with placebo and those with denosumab."

Dr. Rosen asked about absence of detectable CTX – absence of label at Month 36. Dr. Stehman-Breen answered, "There was an absence of label in cortical bone in about a third of the subjects in which we conducted bone biopsies. This is consistent with the mechanism of action of denosumab and the level of suppression that we've seen with CTX…We've not demonstrated any adverse impact of that level of bone turnover reduction as reflected by labeling in terms of atypical fractures or abnormalities and healing of fractures. We are committed to monitor this in the long-term safety program. Additionally, bone biopsies will be conducted as part of that long-term extension study to continue to understand what the bone histomorphology is over the long-term treatment."

Asked if there is anything that can predict which patients might lack a label, Dr. Stehman-Breen said, "No variables have been able to predict those subjects who are going to have a lack of label. It's also consistent with our mechanism of action, so although we could potentially identify a risk factor for lack of label, it ultimately would be most relevant if we found an adverse outcome associated with that level of suppression. It's important to note that denosumab is reversible, so we have an ability to discontinue the therapy." A panel member said, "We are not used to seeing the absence of label in a third of the subjects, so we need some clarification what the importance is. We're not making any judgments." Dr. Stehman-Breen answered, "I understand your concern."

Asked about bone remodeling, an Amgen scientist said that samples from the iliac crest rarely need mechanical repair, "It is not a fracture site…To trigger remodeling, it's very low at that site. So, it is reasonable to assume we could see complete suppression of remodeling at that site." He also said that CTX values overlapped with single and double labels, so even if there is no label in the biopsy, "there is still remodeling occurring at a substantial rate in other parts of the skeleton."

ONJ

Panel member Dr. Michael Collins, chief of the skeletal clinical studies unit at the National Institutes of Health (NIH), asked what Amgen's exit strategy would be if cases of ONJ were found in denosumab patients. Amgen's Dr. Eisenberg said, "We will be acquiring long-term data and giving safety updates that are comprehensive…Should we see a signal, it is reversible." Dr. Collins said, "That is comforting because that isn't the case with the bisphosphonates."

Number needed to treat (NNT)

Dr. Aman Buzdar, an oncologist from the University of Texas MD Anderson Cancer Center, questioned Amgen about side effects, "There are hints of serious side effects. Have you looked at developing some kind of model in which you can predict whether the overall therapy ratio will be favorable – i.e., preventing a major life-changing event like hip fracture, compared to breast cancer or ovarian cancer, for example, which are also life-changing events?"

Dr. Eisenberg answered, "How many lives can we save? That would be presumptuous. But the number needed to treat is actually quite low. One in 30 patients treated will be prevented from having a fracture…Your point is fair – there are potential risks that we have to monitor long term, but none that we can confirm…I think in terms of the skin infection risk we have a little more concern…but none are more than a small difference."

Dr. Buzdar responded, "I am not concerned with skin infections. I'm concerned with ovarian cancer, which is life-threatening and potentially lethal in the majority of patients. We can't see how the data evolve in a decade or two. e should be able to calculate what is the net benefit…You're going to expose a large population to a therapy that has a small but potentially life-changing event. What is the effect in the long run?"

Dr. Eisenberg showed new data indicating that over three years of treatment denosumab would prevent:

- New vertebral fracture: NNT=21
- Non-vertebral fracture: NNT=68
- Hip fracture: NNT=206

Dr. Eisenberg added, "If the rate is 15 per 1,000 for a drug effect, 10 in 1,000 would be prevented in one year, and the number would be 33 over three years." An Amgen oncologist told the panel that a 45-50 NNT would be needed in prostate cancer. Dr. Emerson, a biostatistician, said, "That's for any fracture. Some of your definitions are quite subclinical."

The consumer advocate told Amgen that this information should have been in the original briefing materials.

Dr. Rosen asked about the NNT for the prevention arm, saying that the number of fractures in the prevention arm "was relatively low. You're saying that NNT for low-risk individuals was 33 for denosumab treated individuals? You can't say that." The Amgen oncologist responded, "We're talking hypothetically about a population with a risk of 15 per 1,000." Dr. Rosen then asked, "Why are we only getting the same risk reduction that we have with every other treatment available?" An Amgen investigator answered, "The meta-analysis suggests a 20%-25% reduction in non-vertebral fractures, and it might be a little less in populations with a somewhat lower risk. That's well within the range."

Dr. Rosen then asked, "When we look at risk vs. benefit, and we have 20% non-vertebral fracture reduction and rare events that are not quite statistically significant, like neoplasm, how do you balance those two events? Because this is the crux of the problem. We have rare events occurring because you're studying lots of people, and you have effects similar to other drugs."

- *Amgen investigator:* "This ends up being a clinical judgment about the risk of the patient sitting in front of you based on age, bone density, and given risk increases."
- *Dr. Eisenberg:* "The rates of malignancy are not statistically significant."
- *Dr. Rosen:* "They are rare events, and you'll see them in the 300,000+ follow-up as well."

Patient populations

Asked where the patient populations came from, Amgen answered: 44.9% Western Europe, 34.7% Eastern Europe, 12% Latin America, 7.4% North America, and 1.2% Australia and New Zealand.

PUBLIC WITNESSES

Of the seven public speakers, most spoke emotionlessly about the need for more awareness about osteoporosis, more information, and better treatment options. Only one speaker, Cynthia Pearson of the National Women's Health Network, spoke with conviction in favor of caution.

Public speakers included:

- **Kathleen Cody, executive director of the Foundation for Osteoporosis Research and Education**, called denosumab "another tool" in the fight against osteoporosis.
- A representative from the **National Osteoporosis Foundation** said that there is a continuing need for new, safe, and effective osteoporosis medications.
- **A Maryland woman diagnosed in her 60s with osteoporosis** said that Fosamax permanently damaged her esophagus. She said that her bone density has increased 15% in the three years that she's been taking denosumab.
- **Lauren Glassman**, **a 60-year-old Washington DC lawyer with osteoporosis**, said that she was diagnosed with osteopenia on her 50th birthday. She has a family history of osteoporosis and "was one of the 4% of patients on Forteo (Lilly, teriparatide) who did not show any increase in bone density after two years on the regimen." No other approved medications work, and she told the panel, "For me and others who haven't found something to work, efforts to find and improve new drugs to treat this disease are urgently needed."
- **Gladys Quintero**, a single, retired woman from Arlington VA, spoke of the need for more awareness about osteoporosis.
- **Seth Ginsburg, president of the Global Healthy Living Foundation and Creaky Joints**, a patient advocacy group, said that he has had spondyloarthropathy since he was a teenager. He told the panel that new treatment options are needed.
- **Cynthia Pearson, executive director of the National Women's Health Network**, urged caution with denosumab, "The current FDA guidelines for testing a drug for use by healthy women to reduce risk of fracture in the future only require evidence that the effectiveness of the drug is seen on x-ray. A woman can go into the study with no symptoms and leave with no symptoms, and the FDA can say that there is enough evidence of benefit, using its guidelines. Current screening guidelines that are evidence-based are calling for screening of women starting at age 65. Unfortunately, what we saw in this room with our own FDA is that there is a much too common impression created by very effective marketing campaigns that screening should start at age 50. Many women are getting screened who don't need it, and the FDA…has to find some sort of guidelines…I heard (here with denosumab) evidence of increasing recurrence of breast cancer, increasing occurrence of new cancers, including ovarian and cervical, in postmenopausal women, increasing of serious infections, some of which require hospitalization. Both of these things – cancer and infection – are biologically plausible as a cause and effect. And then there's the possibility of bone problems in the future. The FDA is going to ask you to answer the question, 'Is there a reasonable expectation that benefits outweigh the harm,' and I'd say…no."

PANEL CONSIDERATION OF FDA QUESTIONS

QUESTION 1. Is there a population of postmenopausal women with osteoporosis in which the benefit of *treatment* with denosumab is likely to outweigh the risks?

VOTE: Unanimously Yes

Panel comments included:

- *Dr. Emerson, biostatistician:* "I think separating subgroups would be fraught with peril. In the large trial of 8,000 women, they had a benefit, but the number needed to treat is important to me. To prevent any fracture, you'd have to treat 16. To treat hip or vertebral fractures, it's 18; but (for hip alone) it's hundreds. (There is) roughly a 1.0%-1.5% difference in serious adverse events of every kind. Likely, a decrease in quality of life from the fractures in this population was worse from the fractures than it is from the unknown risks that haven't been quantified. So, for the treatment it's looking like that group would benefit."

- *Dr. Ronald Richardson, assistant professor of oncology at the Mayo Clinic:* "There are a lot of differences among these vertebral fractures…Some are major events fraught with pain, morbidity. We see a lot of guys with loss of height, but they're totally unaware of it. Are you counting those in your vertebral fractures?"
- *Biostatistician:* "Twenty-four percent of these women have had previous fractures."
- *Dr. Rosen, a BMD expert:* "For a bone-active drug this is as good as it gets for vertebral fractures…With numbers needed to treat less than 20, that's pretty impressive…I certainly favor yes on this particular issue…This is a high-risk subgroup, so I think it would be difficult to parcel individual subgroups from that. For the treatment for postmenopausal established osteoporosis, it fits…The way the question is phrased, I would say the answer is yes."
- *Dr. Lawrence Nelson, an endocrinologist from NIH:* "I would say yes."

QUESTION 2. Is there a population of postmenopausal women with low bone mineral density who do not meet the criteria for treatment of osteoporosis in which the benefit of *prevention* of osteoporosis with denosumab is likely to outweigh the risks? If yes, which population.

VOTE: 3 Yes, 12 No

Panel comments included:

- *Panel chair:* "This is basically the same question but for prevention – for women who don't have osteoporosis but have osteopenia…We have seen that this drug does prevent bone mineral density loss, so if we're talking about those numbers, then the answer should be yes. The question is that of safety. When you look at the risk of osteopenia…it does progress to osteoporosis and fracture. So, I think there is some benefit, but then that is when safety becomes important. We have to be conscious of what we're doing long term with safety. Also, when this drug is stopped, bone mineral density does plummet...So, we're talking about long-term therapy, and we'd better be convinced of its safety."
- *Dr. Michael Collins, chief of the skeletal clinical studies unit at NIH:* "The answer is yes, but we don't know who they are."
- *Biostatistician:* "My answer is going to be no…I don't think there is evidence in this group. It was tested in 300 women…I raised my objection to the FRAX 10-year."
- *Dr. Rosen:* "The sponsor did the right study because you only need 300 subjects to show significant effect on bone density. The question is...the uncertainty of treating a large number of people with osteopenia with the risks involved."

QUESTION 3a. For the prevention and treatment of bone loss in patients undergoing hormone ablation for breast cancer, is a favorable risk:benefit demonstrated for denosumab for the *treatment* of bone loss associated with hormone ablation therapy in women with breast cancer receiving aromatase inhibitors?

VOTE: 2 Yes, 13 No

QUESTION 3b. Is a favorable risk:benefit ratio demonstrated for denosumab for the *prevention* of bone loss associated with hormone ablation therapy in women with breast cancer receiving aromatase inhibitors?

VOTE: 14 No, 1 Abstention

Panel comments on these breast cancer indications included:

- *Dr. Robert Gut of Novo Nordisk, the industry representative:* "I have significant concern…(about the) link to the incidence of breast cancer. I have a reservation in this subset of patients until we see more data…Bone loss is not the major thing. Patients have a fatal disease which is breast cancer…You have a therapy which has been evaluated in a patient population which may have adverse outcomes. So, I think that we have to be cautious."
- *Dr. Johnson, a Vermont gynecologist:* "My concern is that they really didn't look at treatment. They had a relatively small population base, relatively normal T-scores, so I'm not sure they're looking at treatment for this group. I'm not sure they addressed the issue of treatment."
- *Dr. David Margolis, a dermatologist from the Hospital of the University of Pennsylvania:* "I don't think changing bone density in this population is really that important an endpoint."
- *Merrill Goozner, consumer representative:* "I was surprised by the lack of discussion about how this drug compares to other drugs that are out there being used in cancer patients, and we were given no data and no commentary on it at all."
- *Dr. Rosen:* "They're not incorrect that there are no non-approved drugs being used for these cancers…I need some reassurance about the data regarding progression of malignancy in this trial. Was there a statistically significant increase in cancer risk?"
- *Panel chair:* "There is a lot of data associated with a lot of different treatments. But our mission is to look at the information at hand about one particular treatment. Does this drug have a favorable risk:benefit ratio?"
- *Biostatistician:* "Have they demonstrated a favorable risk is what I like in this question."

QUESTION 4a. Is a favorable risk:benefit ratio demonstrated for denosumab for the *treatment* of bone loss associated with hormone ablation therapy in men with prostate cancer receiving androgen deprivation therapy?

VOTE: 9 Yes, 4 No, 1 Abstention

Panel comments ***prior to the vote*** included:

- *Biostatistician:* "I computed that it would take about 50 (NNT) in order to prevent any fracture…My fears are that this is a cancer prone to bone activity…I don't think it has been demonstrated." An Amgen expert responded, "The data that we presented were successful and demonstrated robust benefits on BMD. The number needed to treat, of course, is very dependent on the baseline risk for fracture …There's never been a large fracture prevention study done on men in any setting. This is the largest study to date with 1,500 patients and three-year follow-up."
- *Vermont gynecologist:* "Did you look at non-vertebral fractures?" An Amgen scientist answered, "We have the numbers…to show a significant reduction in non-vertebral fractures would require many, many years of follow-up. At least a third of the so-called disease progression adverse events had no corresponding PSA (prostate specific antigen) progression."
- *FDA scientist:* "More data are necessary."
- *Dr. Rosen, endocrinologist:* "I'd like to explore with the sponsor the total fracture incidence in this population. (At baseline) 24% of these men had prevalent vertebral fractures...Is this group of men at high risk for fracture? Is this a high-risk group of individuals who require intervention?" An Amgen scientist responded, "I believe so…the mean T-scores were relatively normal, but it's worth noting the limitations for screening for these men. Eighty percent of the men had either osteopenia or osteoporosis in at least one site."
- *Dr. Buzdar, oncologist:* "Looking at the FDA interpretation of the same data…who do I believe? Is the sponsor more accurate or the FDA?" The panel biostatistician responded, "My interpretation is that the sponsor's data are more accurate."
- *Dr. Joanne Mortimer, an oncologist and professor of medicine at the City of Hope Medical Center in Duarte CA:* "In the current standard of care, these men would not be untreated."
- *NIH endocrinologist:* "That's not true. At NIH in our prostate cancer group, you're hard-pressed to find anything resembling standard of care."

Panel comments ***after the vote*** included:

- *Dr. James Gulley, director of the clinical trials group, Laboratory of Tumor Immunology and Biology:* "I voted yes. The dataset was big, and I thought there was a clear benefit here."
- *Dr. Ronald Richardson, an oncologist at the Mayo Clinic:* "I voted no mainly because the risks haven't been clearly elucidated, and the benefits are modest. A lot of these men have a lot of comorbidities that cloud the issue. When you look at the risks, the risk factors accumulate substantially."
- *California oncologist:* "The risks outweigh the benefits here."
- *Texas oncologist:* "Disease progression is an important issue."
- *NIH endocrinologist:* "I voted yes because the study design was good. I wonder why they didn't have the same kind of design for breast cancer."
- *Dr. Johnson, gynecologist:* "I voted yes. I did think that this was a strong study. It clearly did a lot better job looking at the potential benefit for these cancer survivors …It was a much stronger study than the breast cancer study."
- *Panel chair:* "I voted yes. I was disappointed that I couldn't vote yes in the breast cancer study because there were no hard markers."
- *Dr. Rosen:* "It was a well designed study...We need to have a drug out there that reduces fractures (in this population)."
- *NIH skeletal studies chief:* "My vote is a cautious yes."

QUESTION 4b. Is a favorable risk:benefit ratio demonstrated for denosumab for the *prevention* of bone loss associated with hormone ablation therapy in men with prostate cancer receiving androgen deprivation therapy?

VOTE: 3 Yes, 11 No

Panel comments ***prior*** to the vote included:

- *Dr. Johnson, gynecologist:* "These gentlemen had a pretty normal T-cell but they had fractures. Prevention is a hard thing to determine but this group seemed somewhat unique to me."
- *Dr. Rosen, endocrinologist:* "Spine BMD goes up with age…but 23% of them had vertebral fractures. That's pretty high, and that puts them at high risk. BMD is not the end all, be all. You need clinical judgment to identify people at risk."
- *Panel chair:* "So do you think that men on this therapy should get the drug preventively?"
- *Dr. Rosen:* "They are probably getting therapy anyway, but not at the level of this drug…The way the question is phrased – if they had gone back to the original question: 'Is there a subset (that benefits),' that would be a little more comforting."

- *NIH skeletal studies chief:* "You can see that a drug gets approved, and it gets given to everybody. I guess that's not our concern."
- *Panel chair:* "That's probably why this question is quite global and inclusive."
- *Dr. Buzdar, oncologist:* "We are being asked if it's a favorable benefit:risk ratio, and that question has not been answered completely…I think if you look at the other side of the coin, the answer is no."
- *Dermatologist:* "We have to look at what the study was designed to show. It was designed to treat people already sick and not someone just diagnosed…If there is any suspicion that there's an increased risk of cancer recurrence, it is not worth it, and that is incredible risk."
- *Dr. Rosen:* "You can't say globally that everyone is at risk…If they lost absolute bone, I would treat them."
- *NIH endocrinologist:* "I think if you do get evidence that they are deteriorating, we should be able to use this for prevention before they get to osteoporosis."

Panel comments ***after*** the vote:

- *NIH skeletal studies chief:* "We have remaining questions about safety."
- *Dr. Rosen:* "Dr. Mortimer scared me, and I think that some of her points from the other side of the room are correct; and when we talk about prevention, it's different than treatment."
- *Panel chair:* "I think this does produce bone density, and I am so sad to see this same study not duplicated in women."
- *NIH endocrinologist:* "I was going to vote yes right up until the last minute, and the reason I voted no – let's get some data that the bone density is declining, and then let's treat it."
- *Dermatologist:* "We still need a prevention study."
- *Mayo clinic oncologist:* "The safety concerns are real with this drug. When it comes to the issue of prevention, when you look at the use of zoledronic acid in the medical oncology field, everyone has revisited that particular drug with respect to schedule and how it's used. For some reason this got into the monthly type of regimen. Everyone has taken a second look at that. If you're treating osteoporosis in these men, you treat them once a year."
- *Panel chair:* "The committee voted against there being a favorable benefit:risk ratio for prevention…There was not evidence as to the drug's safety in patients with prostate cancer and that this possible risk did not justify the issue of not being able to precisely choose in which patients this drug would prevent bone loss."
- *Vermont gynecologist:* "I want to wait a bit before we use this for prevention."
- *MD Anderson oncologist:* "It has not shown that it is safe, and it has no adverse effect on the outcome of the disease."

QUESTION 5. Prior to approval of an indication for treatment or prevention of bone loss in patients with cancer receiving hormone ablation, should the data from studies designed to evaluate the effects of denosumab on skeletal related events (bone metastases) in advanced cancers be required to be submitted to the FDA for review to determine if there are any detrimental effects on cancer outcomes (PFS, OS)?

This is the question that the FDA's Dr. Jenkins wanted to change. After discussion, the panel decided not to deal with this question, original or revised.

QUESTION 6a. If approved, do you recommend that denosumab have a REMS?

VOTE: 12 Yes, 1 No

Many panel members did not know how to discuss this question. One panel member asked if they could get input from the company on how it felt about it (and was told no). Another panel member didn't know the difference between a medication guide and a communication plan. The biostatistician asked, "The company has presented a post-marketing surveillance plan, and how is this different from what the company has proposed?" An FDA official responded, "The medication guide and communication plan have to do with communicating risk to prescribers and patients. It doesn't have to do with assessing risk."

Panel comments after the vote included:

- *Dr. Gulley, immunologist:* "When there is potential for a safety signal, it's important to have informed people."
- *Panel chair:* "I voted no because I don't think that there is evidence that REMS are helpful and just not costly."
- *Biostatistician:* "It's not clear to me whether this bang is worth the buck."
- *Dr. Rosen, endocrinologist:* "It's important, especially with a first-in-class drug."

QUESTION 6b. If so, which elements should be included in a REMS?

- **A medication guide to inform patients about the risks of the drug? The consensus was Yes.**
- **A communication plan to disseminate information to healthcare providers? The consensus was Yes.**

➢ **Other? Although a few panel members, including the chair, did not want a REMS, saying that it was too costly, the panel generally agreed (without voting) to suggest a registry.**

Panel comments on what should be in a REMS included:

- *Consumer rep:* "The idea that we're going to be giving a shot in an office, and we can't record who got it and what happened…strikes me as like a $1.38 in today's electronic environment unless you don't have an electronic environment. I don't know if this is the right drug to have a registry for, but it seems to be the kind of drug that you could easily have a registry for…One of the things we see over and over again is the lack of data…REMS are fairly new…We, as advisers, should articulate that there is a new world coming in medicine, and we should be able to gather a lot more information about a lot of drugs, and we should articulate that vision here."
- *Vermont gynecologist:* "This is so new and unique, and a lot of things said today reflected our concerns about this medication. Although the studies were well-designed, it is important to get more information about the long-term effects."
- *NIH endocrinologist:* "I also like the idea of a registry."
- *Panel chair:* "The committee suggested recommending a REMS, that perhaps a registry be a strategy as well as a patient information guide and a communication plan for disseminating information to practitioners."

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