U.S. Food and Drug Administration

Notice: Archived Document

The content in this document is provided on the FDA's website for reference purposes only. It was current when produced, but is no longer maintained and may be outdated.

Summary Minutes of the
Advisory Committee for Reproductive Health Drugs
August 13, 2009

Location: Hilton Washington DC North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for the August 13, 2009 Meeting of the Advisory Committee for Reproductive Health Drugs of the Food and Drug Administration were approved on __August 17, 2009.

I certify that I attended the August 13, 2009, Meeting of the Advisory Committee for Reproductive Health Drugs of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____	**_____/s/_____**
Kalyani Bhatt	Sandra Carson, M.D.
Designated Federal Official, ACHRD	Committee Chair

Final Summary Minutes
Advisory Committee for Reproductive Health Drugs Meeting
August 13, 2009

The Advisory Committee for Reproductive Health Drugs of the Center for Drug Evaluation and Research met on August 13, 2009 at the Hilton Washington DC North/Gaithersburg, Maryland The Ballrooms, 620 Perry Parkway, Gaithersburg, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. This was a voting meeting. There were approximately two hundred (200) persons in attendance.

Issue: Agenda: The committee will discuss new biologics license applications (BLAs) 125-320, 125-331, 125-332, and 125-333, proposed trade name PROLIA (denosumab) subcutaneous injection, 60 milligrams (mg), Amgen Inc., for the proposed indications of the treatment and prevention of osteoporosis in postmenopausal women, and the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer. Hormone ablation is a term used to encompass therapies for hormone sensitive breast or prostate cancer administered to decrease sex hormone (estrogen or testosterone) levels. These therapies can result in increased bone loss.

Attendance:

Advisory Committee for Reproductive Health Drugs (Voting):
Sandra Carson, M.D., Julia V. Johnson, M.D.

Industry Representative Member Present (Non-Voting): Robert Gut, M.D., Ph.D.

Special Government Employee Consultants (Voting):
Aman U. Buzdar, M.D., John Bennett, M.D., Michael T. Collins, M.D., Scott Emerson, M.D., Ph.D., Merrill Goozner *(Acting Consumer Representative)*, James L Gulley, M.D., Ph.D., FACP, David J. Margolis, M.D., Ph.D., Joanne E. Mortimer, M.D., FACP, Lawrence M. Nelson, M.D., Ronald Richardson, M.D., Clifford J. Rosen, M.D., Martha Solonche (Patient Representative), Gulbu Uzel, M.D.

FDA Participants (Non-Voting): Julie Beitz, M.D., George Benson, M.D., Suzanne Demko, P.A.-C, Theresa Kehoe, M.D., Richard Pazdur, M.D.

Designated Federal Official: Kalyani Bhatt, BS, MS

Open Public Hearing Speakers:

Kathleen Cody, Executive Director
Foundation for Osteoporosis Research and Education dba American Bone Health
Roberta Biegal, National Osteoporosis Foundation
Marilyn Brown
Gladys Quinterro
Laurel Glassman, Attorney
Cindy Pearson, National Women's Health Network

AGENDA

Call to Order and Introductions	Sandra Carson, M.D., Chair Advisory Committee for Reproductive Health Drugs (ACRHD)
Conflict of Interest Statement	Kalyani Bhatt, B.S., M.S. Designated Federal Official, ACRHD
Introduction	George Benson, M.D. Director, Division of Reproductive and Urologic Products (DRUP)
Sponsor Presentation	Amgen, Inc.
Introduction	Paul Eisenberg, MD, MPH Senior Vice President Global Regulatory Affairs & Safety Amgen Inc
Burden of Disease and Need for Improved Therapy in Postmenopausal Osteoporosis (PMO) and Hormone Ablation Therapy (HALT)	Ethel Siris, MD Columbia University Medical Center, New York Presbyterian Medical Center Immediate Past President, National Osteoporosis Foundation
Discovery of RANK Ligand and Development of Denosumab	David Lacey, MD Senior Vice President Research Amgen Inc

Denosumab Clinical Efficacy and Safety Assessments: PMO & HALT	Catherine Stehman-Breen, MS, MD Vice President Global Development Amgen Inc
Denosumab Pharmacovigilance Plan: PMO & HALT	Paul Eisenberg, MD, MPH Senior Vice President Global Regulatory Affairs & Safety Amgen Inc

FDA Presentation

Denosumab Efficacy Analysis	Vaishali Popat, MD Medical Officer, DRUP
Denosumab Safety Analysis	Adrienne Rothstein, PharmD Clinical Analyst, DRUP
Bone Histomorphometry Denosumab Safety Summary Summary of Risks and Benefits of Denosumab Therapy	Theresa Kehoe, MD Clinical Team Leader, DRUP

Questions to the Presenters

Lunch

Open Public Hearing

Questions to the Presenters

Questions to ACRHD

Adjournment

Questions to the Committee

Benefit/Risk Profile – Treatment of postmenopausal osteoporosis

Question 1a [Vote: Yes/No]: Is there a population of postmenopausal women with osteoporosis in which the benefit of treatment with denosumab is likely to outweigh the risks?

Yes-15 *No-0* *Abstain-0*

The committee favorably voted that there is a population of postmenopausal women with osteoporosis in which the benefit of treatment with denosumab is likely to outweigh the risks.

Question 1b [Discussion]: If yes, would this population be:

(1) all women with postmenopausal osteoporosis,
(2) limited to a subgroup at a high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or women who have failed or are intolerant to other osteoporosis therapies osteoporotic fracture

The committee has come to a consensus that there is a benefit to giving denosumab in a sub-population of women with postmenopausal osteoporosis. The committee's consensus is that the drug should be limited to a subgroup with a high risk for fracture, with history of osteoporotic fracture as well as patients that have failed, or are intolerant, of other therapeutic measures.

Benefit/Risk Profile – Prevention of postmenopausal osteoporosis

Question 2a [Vote: Yes/No]: 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?

Yes-3 *No-12* *Abstain-0*

The committee consensus was that there is not a population of postmenopausal women with
low bone mineral density who meet the criteria for the treatment osteoporosis in which the benefit of prevention of osteoporosis with denosumab is likely to outweigh the risks. The committee's consensus was that although this treatment may be effective, it is related to unknown risks which may not make the benefit of prevention worth while.

Question 2b [Discussion]: If yes, which population?

Benefit/Risk Profile – Prevention and Treatment of bone loss in patients undergoing hormone ablation for breast cancer

The committee voted NO.

Question 3a [Vote: Yes/No]: Is a favorable risk/benefit ratio demonstrated for denosumab for the treatment of bone loss associated with hormone ablation therapy in women with breast cancer receiving aromatase inhibitors?

Yes-2 *No- 13* *Abstain-0*

The committee voted against a favorable risk/benefit ratio demonstrated for denosumab for the treatment of bone loss associated with hormone ablation therapy in women with breast cancer receiving aromatase inhibitors.

Question 3b [Vote: Yes/No]: 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?

Yes-0 *No-14* *Abstain- 1*

The committee consensus is that there is not 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. The committee had concerns that long term safety of treatment was not demonstrated, especially with respect to progression of the breast cancer.

Benefit/Risk Profile – Prevention and Treatment of bone loss in patients undergoing hormone ablation for prostate cancer

Question 4a: [Vote: Yes/No]: 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?

Y*es-9* *No-4* *Abstain-1* *Not voting-Emerson*

The committee voted that there 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. Efficacy was demonstrated in reducing fractures and the safety risk was demonstrated with hard markers, not surrogates.

Question 4b: [Vote: Yes/No]: 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?

Yes-3 *No-11* *Abstain-0* *Not voting-Emerson*

*The committee did not feel that a **favorable** risk/benefit ratio was demonstrated for denosumab for the prevention of bone loss associated with hormone ablation therapy in men with prostate cancer receiving androgen deprivation therapy.*

The possible risk did not justify use as there is no data to identify the subgroup most likely to have a decline in Bone Mineral Density (BMD).

Cancer Progression and All-Cause Mortality

Background: The Office of Oncology Drug Products requires that supportive care products for patients with cancer be carefully evaluated in studies to identify any potential for detrimental effects on cancer outcomes [progression free survival (PFS) or overall survival (OS)] prior to allowing labeling claims. Neither trial submitted in support of this BLA included time-to-event endpoints. There were no routine neoplastic disease assessments included in Trial 135 (women with breast cancer). Trial 138 (men with prostate cancer) included disease assessments only as related to metastatic disease to bone (i.e., bone scan at baseline and month 36), and disease specific markers (i.e., PSA at all time points during the treatment phase).

In both trials, overall survival (at 24 months in Trial 135 and 36 months in Trial 138) was a designated exploratory endpoint. However, neither trial was designed with a survival endpoint in mind. No OS analysis was performed in trial 135 because of the small number of events (one in each group). Trial 138 included an exploratory analysis of OS. There was no difference observed in overall survival between the treatment groups. The proportion of subjects who were alive at 36 months (denosumab 94%, and placebo 93%) and the Kaplan-Meier estimates of survival were nearly identical. There were not enough events in either trial for meaningful analyses.

Question 5 [**Vote: Yes/No]:** 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 Agency for review to determine if there are any detrimental effects on cancer outcomes (PFS, OS)?

No vote was taken on Question 5. The Committee indicated that studies should show safety, with no adverse outcome on clinical course of cancer treatment.

Risk Evaluation and Mitigation Strategies

Question 6a [Vote: Yes/No]: If approved, do you recommend that denosumab have a Risk Evaluation and Mitigation Strategy or REMS?

Yes-12 No-1 Abstain-0 Not Voting-Emerson
Mortimer

The committee recommended denosumab have a Risk Evaluation and Mitigation Strategy or REMS. The consensus was that any education piece to inform practioners would be beneficial.

Question 6b [Discussion]: If so, which elements should be included in the REMS?

(1) A Medication Guide to inform patients about the risks of the drug?
(2) A Communication Plan to disseminate information to healthcare providers?
(3) Other?

The committee felt that both a Medication Guide to inform patients about the risks of the drug and a Communication Plan is needed in order to disseminate information to healthcare providers. A registry and a patient information guide could be part of the strategy.

The meeting adjourned at approximately 5:00 PM