FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE REPRODUCTIVE HEALTH DRUGS AND DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEES

FRIDAY, SEPTEMBER 9, 2011

8:00 a.m. to 4:30 p.m.

Marriott Inn and Conference Center

University of Maryland University College (UMUC)

3501 University Boulevard

Adelphi, Maryland

1 **Meeting Roster**

2 **ACTING DESIGNATED FEDERAL OFFICER**

3 **(Non-Voting)**

4 **Yvette Waples, Pharm.D.**

5 Division of Advisory Committee and Consultant

6 Management

7 Office of Executive Programs

8 Center for Drug Evaluation and Research

9

10 **ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS**

11 **MEMBERS (Voting)**

12 **Bart Clarke, M.D.**

13 Associate Professor of Medicine

14 Mayo Clinic College of Medicine

15 Department of Medicine, Endocrinology,

16 Diabetes, Metabolism and Nutrition

17 Rochester, Minnesota

18

19

20

21

22

1 **Kathleen Hoeger, M.D., M.P.H.**
2 Associate Professor of OB/GYN
3 Director, Division of Reproductive
4 Endocrinology
5 University of Rochester Medical Center
6 Rochester, New York
7
8 **John Kittelson, Ph.D.**
9 Department of Biostatistics and Informatics
10 University of Colorado Denver
11 Aurora, Colorado
12
13 **Michele Orza, Sc.D.**
14 ***(Consumer Representative)***
15 Public Health
16 Principal Policy Analyst
17 National Health Policy Forum
18 George Washington University
19 Washington, District of Colombia
20
21
22

1 **ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS**

2 **MEMBER (Non-Voting)**

3 **Robert Gut, M.D., Ph.D.**

4 ***(Industry Representative)***

5 Vice President, Clinical Development &

6 Medical Affairs

7 Biopharmaceuticals

8 Novo Nordisk Inc.

9 Medical Department

10 Princeton, New Jersey

11

12 **William Cooper, M.D., M.P.H.**

13 Professor of Pediatrics and Preventive Medicine

14 Departments of Pediatrics and Preventive

15 Medicine

16 Vanderbilt University School of Medicine

17 Nashville, Tennessee

18

19

20

21

22

Brian Erstad, Pharm.D.
Professor
University of Arizona College of Pharmacy
Department of Pharmacy Practice & Science
Tucson, Arizona

Sonia Hernandez-Diaz, M.D., Dr.PH.
Associate Professor
Department of Epidemiology
Harvard School of Public Health
Boston, Massachusetts

David Madigan, Ph.D.
Professor, Chair, Department of Statistics
Columbia University
New York, New York

Elaine Morrato, Dr.PH.
Assistant Professor
Department of Pediatrics
University of Colorado Denver
Aurora, Colorado

1 **Lewis Nelson, M.D.**
2 Director, Fellowship in Medical Toxicology
3 New York University School of Medicine
4 New York, New York
5
6 **Maria Suarez-Almazor, M.D., Ph.D.**
7 Barnts Family Distinguished Professor
8 University of Texas MD Anderson Cancer
9 Center
10 Houston, Texas
11
12 **Allen Vaida, Pharm.D., FASHP**
13 Executive Vice President
14 Institute for Safe Medication Practices
15 Horsham, Pennsylvania
16
17
18
19
20
21
22

1 **Almut Winterstein, Ph.D.**
2 Associate Professor
3 Department of Pharmaceutical Outcomes and
4 Policy
5 College of Pharmacy
6 Department of Epidemiology
7 Colleges of Medicine and Public Health
8 Director, FDA/CDER Graduate Program in
9 Pharmaceutical Outcomes Research
10 University of Florida
11 Gainesville, Florida
12
13 **T. Mark Woods, Pharm.D.**
14 Clinical Coordinator and Residency
15 Program Director
16 Pharmacy Department
17 Saint Luke's Hospital
18 Kansas City, Missouri
19
20
21
22

TEMPORARY MEMBERS (VOTING)

Kenneth Burman, M.D.

Chief, Endocrine Section

Washington Hospital Center

Professor, Department of Medicine

Georgetown University

Washington, District of Columbia

Sandra Ann Carson, M.D. (Acting Chair)

Professor of Obstetrics and Gynecology

Alpert Medical School of Brown University

Director, Division of Reproductive

Endocrinology and Infertility

Women and Infants Hospital of Rhode Island

Providence, Rhode Island

1 **Michael Collins, M.D.**
2 Chief, Skeletal Clinical Studies Unit
3 Craniofacial and Skeletal Diseases Branch
4 National Institute of Dental and Craniofacial
5 Research
6 National Institutes of Health
7 Bethesda, Maryland
8
9 **William Duncan, M.D, Ph.D.**
10 Associate Deputy Under Secretary for Health for
11 Quality and Safety
12 Department of Veterans Affair
13 Washington, District of Columbia
14
15 **Julia Johnson, M.D.**
16 Professor and Chair
17 Department of Obstetrics and Gynecology
18 University of Massachusetts Medical School
19 UMass Memorial Campus
20 Worcester, Massachusetts
21
22

1 **Karla Miller, M.D.**
2 Assistant Professor
3 University of Utah
4 Division of Rheumatology
5 School of Medicine
6 Salt Lake City, Utah
7
8 **Clifford Rosen, M.D.**
9 Director of Center for Clinical and Translational
10 Research
11 Maine Medical Center Research Institute
12 Scarborough, Maine
13
14 **Mary Ruppe, M.D.**
15 Assistant Professor
16 The University of Texas Health Science Center
17 at Houston
18 Houston, Texas
19
20 **Elizabeth Tucker**
21 ***(Patient Representative)***
22 Lakeville, Minnesota

1 **GUEST SPEAKER (Non-Voting, Presenting Only)**

2 **Douglas C. Bauer, M.D.**

3 Professor of Medicine and Epidemiology &

4 Biostatistics

5 University of California, San Francisco

6 San Francisco, California

7

8 **SPEAKER (Non-Voting, Presenting Only)**

9 **Robert A. Adler, M.D.**

10 Professor of Internal Medicine

11 Professor of Epidemiology and Community Health

12 Virginia Commonwealth University School of Medicine

13 Chief, Endocrinology and Metabolism

14 McGuire Veterans Affairs Medical Center

15 Richmond, Virginia

16

17 **FDA PARTICIPANTS (Non-Voting)**

18 **Julie Beitz, M.D.**

19 Director, Office of Drug Evaluation III

20 Office of New Drugs,

21 Center for Drug Evaluation and Research

22

George Benson, M.D.

Deputy Director, Division of Reproductive and Urologic Products

Theresa Kehoe, M.D.

Medical Officer Team Leader, Division of Reproductive and Urologic Products

Marcea Whitaker, M.D.

Medical Officer, Division of Reproductive and Urologic Products

Judy Staffa, Ph.D., R.Ph.

Director, Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Fatmatta Kuyateh, M.D., M.S.

Medical Officer, Division of Epidemiology II

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order and Opening Remarks

Introduction of Committees

DR. CARSON: Good morning and welcome. My name is Sandy Carson. I'm the acting chair of the Advisory Committee for Reproductive Health Drugs, and I will now call the joint meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee to order.

I would first like to remind everyone to please silence your cell phones, BlackBerrys, PDAs, and other devices that make noise if you have not already done so. I would also at this point like to identify FDA press contacts, Mr. Jeff Ventura and Ms. Yolanda Fultz-Morris. If you are present, please stand.

Okay. Right at the door. Great.

We will now go around the room and introduce panel members. Let's start with the FDA and Dr. Julie Beitz to my left, and go around the

table.

DR. BEITZ: Good morning. I'm Julie Beitz, the director of the Office of Drug Evaluation III in CDER, FDA.

DR. STAFFA: Good morning. I'm Judy Staffa. I'm the director of the Division of Epidemiology II in the Office of Surveillance and Epidemiology, CDER, FDA.

DR. BENSON: I'm George Benson, deputy director of the Division of Reproductive and Urologic Products.

DR. KEHOE: Theresa Kehoe, clinical team leader for the Reproductive and Urologic Products.

DR. WHITAKER: Good morning. I'm Marcea Whitaker, a medical reviewer in the Division of Reproductive and Urologic Products.

DR. KUYATEH: Good morning. Fatmatta Kuyateh, medical officer within the Division of Epidemiology.

DR. DUNCAN: Good morning. Bill Duncan, Associate Deputy Under Secretary for Health for Quality and Safety at the Veterans Administration.

DR. RUPPE: I'm Mary Ruppe. I'm an assistant professor of medicine at the University of Texas Health Science Center in Houston.

DR. COLLINS: Good morning. Michael Collins. I'm chief of the Clinical Skeletal Studies Unit at the National Institutes of Health.

DR. ROSEN: I'm Cliff Rosen. I'm at Maine Medical Center Research Institute.

DR. BURMAN: Ken Burman, chief of endocrinology at the Washington Hospital Center and professor of medicine at Georgetown.

DR. KITTELSON: John Kittelson, professor of biostatistics at the University of Colorado Denver.

DR. HOEGER: Kathleen Hoeger, professor of obstetrics and gynecology at the University of Rochester.

DR. CLARKE: Bart Clarke, associate professor of medicine, Mayo Clinic, Rochester, Minnesota.

DR. ORZA: Michele Orza, principal policy analyst at the National Health Policy Forum at George Washington University.

DR. CARSON: I'm Sandy Carson. I'm a professor of obstetrics and gynecology at the Alpert Medical School at Brown University, and I'm a reproductive endocrinologist.

DR. WAPLES: Yvette Waples. I'm the acting designated federal officer for this meeting.

MS. TUCKER: Elizabeth Tucker. I'm the patient representative, from Minneapolis, Minnesota.

DR. WOODS: Good morning. My name is Mark Woods. I'm the clinical pharmacy coordinator and residency program director in the pharmacy department at Saint Luke's Hospital in Kansas City, Missouri.

DR. MORRATO: Good morning. I'm Elaine Morrato. I'm associate director of the Children's Outcomes Research Program and assistant professor in health systems management and policy at the University of Colorado Denver.

DR. WINTERSTEIN: Good morning. I'm Almut Winterstein. I'm an associate professor in pharmacoepidemiology at the University of Florida.

DR. MADIGAN: Good morning. I'm David Madigan. I'm the professor and chair of statistics at Columbia University in New York City.

DR. VAIDA: Good morning. Alan Vaida, executive vice president at the Institute for Safe Medication Practices. I'm a pharmacist.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz, associate professor of epidemiology at Harvard School of Public Health in Boston.

DR. SUAREZ-ALMAZOR: Good morning. Maria Suarez-Almazor. I'm professor of medicine and chief of rheumatology at the University of Texas MD Anderson Cancer Center.

DR. ERSTAD: Good morning. Brian Erstad. I'm with the College of Pharmacy at the University of Arizona, with clinical responsibilities at our medical center.

DR. NELSON: Lewis Nelson. I'm an emergency physician and a medical toxicologist at New York University School of Medicine.

DR. COOPER: Bill Cooper, professor of pediatrics and preventive medicine at Vanderbilt

University.

DR. JOHNSON: I'm Julia Johnson. I'm a reproductive endocrinologist, and I'm professor and chair of the department of OB/GYN at the University of Massachusetts.

DR. MILLER: Good morning. I'm Karla Miller. I'm assistant professor, University of Utah, Division of Rheumatology.

DR. GUT: Good morning. I'm Robert Gut, industrial representative. I am vice president, clinical development and medical affairs, at Novo Nordisk.

DR. CARSON: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look

forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about this topic at hand are placed in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of the meeting with the media until its completion.

Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or during lunch. Thank you. And I will be reminding you of this frequently throughout the day.

LCDR Yvette Waples will read the conflict of interest statement.

Conflict of Interest Statement

DR. WAPLES: Thank you.

The Food and Drug Administration, FDA, is convening today's meeting of the Advisory Committee

1 for Reproductive Health Drugs and the Drug Safety
2 and Risk Management Advisory Committee under the
3 authority of the Federal Advisory Committee Act of
4 1972. With the exception of the industry
5 representative, all members and temporary voting
6 members of the committees are special government
7 employees or regular federal employees from other
8 agencies and are subject to federal conflict of
9 interest laws and regulations.
10 The following information on the status of
11 the committees' compliance with federal ethics and
12 conflict of interest laws, covered by, but not
13 limited to, those found at 18 USC Section 208 and
14 Section 712 of the Federal Food, Drug & Cosmetic
15 Act is being provided to participants in today's
16 meeting and to the public.
17 FDA has determined that members and
18 temporary voting members of the committees are in
19 compliance with federal ethics and conflict of
20 interest laws. Under 18 USC Section 208, Congress
21 has authorized FDA to grant waivers to special
22 government employees and regular federal employees

1 who have potential financial conflicts when it is
2 determined that a agency's need for a particular
3 individual's services outweighs his or her
4 potential financial conflicts of interest.
5 Under Section 712 of the FD&C Act, Congress
6 has authorized FDA to grant waivers to special
7 government employees and regular federal employees
8 with potential financial conflicts when necessary
9 to afford the committees essential expertise.
10 Related to the discussion at today's
11 meeting, members and temporary voting members of
12 the committees have been screened for potential
13 financial conflicts of interest of their own, as
14 well as those imputed to them, including those of
15 their spouses or minor children, and, for purposes
16 of 18 USC Section 208, their employers. These
17 interests may include investments, consulting,
18 expert witness testimony, contracts, grants,
19 CRADAs, teaching, speaking, writing, patents and
20 royalties, and primary employment.
21 At today's meeting, the committees will
22 discuss the benefits and risks of long-term

1 bisphosphonate use for the treatment and prevention
2 of osteoporosis in light of the emergence of safety
3 concerns of osteonecrosis of the jaw and atypical
4 femur fractures that may be associated with long-
5 term use of bisphosphonates.
6 Bisphosphonates for the treatment and
7 prevention of osteoporosis include Fosamax
8 (alendronate sodium) tablets and solution and
9 Fosamax Plus D (alendronate sodium/cholecalciferol)
10 tablets; Merck & Company, Actonel (risedronate
11 sodium) tablets; Atelvia (risedronate sodium)
12 delayed release tablets; and Actonel with calcium,
13 copackaged, (risedronate sodium with calcium
14 carbonate) tablets; Warner Chilcott, Boniva
15 (ibandronate sodium) tablets and injection; Roche
16 Therapeutics, Reclast (zoledronic acid) injection;
17 Novartis Pharmaceuticals and the generic
18 equivalents for these products, if any. This issue
19 has been categorized as a particular matter of
20 general applicability.
21 Based on the agenda for today's meeting and
22 all financial interests reported by the committees'

members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they may have concerning the products at issue.

With respect to FDA's invited guest speakers, we would like to disclose that Dr. Douglas Bauer has acknowledged current professional and financial relationships with Novartis and Amgen, as well as past professional and financial relationships with Merck and Roche Diagnostics. Novartis, Merck, and Roche are all sponsors of bisphosphonate products that are the topic of today's meeting. Amgen markets a competing product.

Dr. Robert Adler, a full-time federal employee of McGuire Veterans Administration Medical Center, was a member of the Atypical Femur Fractures Task Force. The task force was convened by the American Society of Bone and Mineral

1 Research in the wake of the growing concern about
2 the connection between bisphosphonates and unusual
3 femur fractures. The task force called for
4 additional product labeling, better identification
5 and tracking of patients experiencing these breaks,
6 and more research to determine whether and how
7 these drugs caused the serious but uncommon
8 fractures.
9 Dr. Adler will be presenting the practicing
10 clinician's dilemma regarding how long to treat
11 with bisphosphonates. Dr. Adler is not
12 representing the task force or the American Society
13 of Bone and Mineral Research. Additionally, he
14 will not be participating in the panel discussion
15 of the benefits and risks of long-term
16 bisphosphonate use.
17 With respect to FDA's invited industry
18 representative, we would like to disclose that
19 Dr. Robert Gut is participating in this meeting as
20 a nonvoting industry representing acting on behalf
21 of regulated industry. Dr. Gut's role at this
22 meeting is to represent industry in general and not

any particular company. Dr. Gut is employed by Novo Nordisk, Incorporated.

We would like to remind members and temporary voting members that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firms at issue.

Thank you.

DR. CARSON: We will now proceed with opening remarks from Dr. George Benson, who's with FDA's Division of Reproductive and Neurologic Products. Dr. Benson will also introduce our first speaker. And I would at this time like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate unless at the

specific request of the panel.

Dr. Benson?

Opening Remarks

DR. BENSON: Good morning. We would like to thank Dr. Carson and the members of the advisory committee and our speakers for their time and effort and for their contributions to the discussion of an important public health issue. Today we will be discussing considerations in the use of bisphosphonates for the prevention and treatment of osteoporosis.

The numbers of patients with osteoporosis and the numbers of patients currently taking bisphosphonates are considerable. Potential safety concerns, several of them uncommon or rare events, have emerged with the more widespread and long-term use of bisphosphonates.

Today we will be discussing bisphosphonates as a class. There are considerable efficacy and safety data relating to the use of this drug class for the first three to five years of therapy. Bisphosphonates are clearly effective in reducing

1 fracture risk, as demonstrated in controlled
2 clinical trials.
3 With the emergence of potential safety
4 concerns, notably atypical femur fractures,
5 osteonecrosis of the jaw, and most recently,
6 esophageal cancer, and the fact that
7 bisphosphonates have a very long dwell time in
8 bone, the need for long-term therapy has been
9 questioned.
10 The members of today's advisory committee
11 will be asked to render their opinions on the
12 optimum duration of use to provide continued
13 efficacy and whether the safety concerns seen
14 primarily in the postmarketing experience impact
15 the long-term use of these drugs. This task is
16 made difficult because of the relative paucity of
17 data related to both the long-term efficacy and to
18 the potential safety concerns which have emerged.
19 The first speaker today is Dr. Robert Adler
20 from the McGuire Veterans Affairs Medical Center
21 and the Virginia Commonwealth University in
22 Richmond. He will present an overview of the

1 challenges currently facing physicians regarding
2 how long to treat patients with bisphosphonates.
3 Dr. Adler?
4 **Speaker Presentation - Robert Adler**
5 DR. ADLER: Good morning, everyone. Thank
6 you very much.
7 These are my affiliations, but please note
8 that the views I am going to present today are my
9 own. These are my disclosures. I receive no
10 salary support from any of this research support.
11 So all of us can agree that osteoporosis is
12 a big problem. There are at least a million and a
13 half osteoporotic fractures each year. I think we
14 all can also agree that from the registration
15 trials, bisphosphonates decreased the risk of
16 fracture, decreased the risk of vertebral fractures
17 somewhere in the 40 to 70 percent range,
18 nonvertebral fractures, about a quarter to 40
19 percent of them. And the most deadly fractures,
20 the hip fracture, 40 to 50 percent are prevented or
21 have been prevented in the randomized, controlled
22 trials.

So we have a big problem, and we have drugs that work. I have to tell my patients, however, that we have no magic bullet, that our drugs decrease the risk of fracture, but we have nothing that eliminates fracture.

These are the FDA-approved indications that all of you know, that alendronate is FDA-approved for osteoporosis in women and men and for glucocorticoid-induced osteoporosis; risedronate, the same indications. Ibandronate is approved for osteoporosis in women; zoledronic acid approved for osteoporosis in women and men, for glucocorticoid-induced osteoporosis, and for secondary fracture prevention.

But it really comes down to the patients, the patients that I see before me every day, that I'm sitting across from, and for whom I have to make decisions today, not waiting five years till all the data is in but what I have to do today. And the first patient that I evaluated recently was a man who was found to have a compression fracture and rib fractures found on an X-ray because he's

got chronic obstructive pulmonary disease.

Unfortunately, he's still smoking. He drinks more than 3 units of alcohol a day. He has a history of Zenker's diverticulum and has gastroesophageal reflux disease that's not under great control. He's about normal size, and when we did his bond density by DEXA, his spine T-score was minus 1.4, femoral neck was minus 2.2, and in the forearm is minus 2.9. So we had low bone mass, or what's been called osteopenia, in his spine, and he had osteoporosis in the forearm.

We used the World Health Organization Fracture Risk Calculator, known as FRAX, to determine what his 10-year fracture rate might be. And with this, he had a 17 percent chance of any fracture, any major osteoporotic fracture, and he had an 8.1 percent hip fracture in the next 10 years. By a cost-effective analysis, it's been suggested that it is cost-effective to treat those patients who have a 3 percent hip risk factor over 10 years because of the significant morbidity, mortality, and cost of hip fracture.

Now, there's one validation study from Australia that suggests that FRAX may actually underestimate the hip and all fracture risks in men, and so I use the Garvan nomogram, which comes from the Dubbo study in Sydney, Australia. And by this fracture risk calculator, this patient had a 55 percent chance of any major osteoporotic fracture in the next 10 years, and an 11.4 percent hip fracture in 10 years.

So as I said, there's some evidence that this particular risk calculator is better for men than is FRAX. But certainly, by either one of those fracture risk calculators, this is a man at high risk.

The second patient is a woman that I evaluated recently. She had had surgical menopause at age 30 and had a gastric bypass at age 52. She had a remarkable loss of weight, more than 200 pounds, although she's gained some of it back. And when we did her DEXA, her femoral neck was minus 2.8. She had osteoporosis by definition.

Even though we usually reserve FRAX for

1 patients with osteopenia or low bone mass, I put
2 her numbers into the FRAX calculation as well. And
3 her hip fracture risk in 10 years was 3.1 percent,
4 again above that 3 percent threshold that's thought
5 to be cost-effective for treating patients who have
6 osteoporosis and increased fracture risk. But her
7 life expectancy is greater than 10 years. She's
8 only 60 years old. And although she's had things
9 happen to her, we have to think she's got a
10 significant risk for 10 years. But she probably
11 has quite a bit more risk as she ages because she
12 is likely to live well beyond 70.
13 So these are the kinds of patients that I
14 see every day, and I have to make a decision, with
15 them, I hope. Some of my patients are of old
16 school and will do what the doctor tells them. A
17 lot of the others bring in stacks of papers from
18 the internet with all sorts of things that they've
19 found. So it varies. But I try to come to a good
20 decision. And I do this with every drug, when you
21 think about it; what are the risks and what are the
22 benefits? Here we know some of the answers, but

obviously we don't know them all.

So the dilemmas facing the clinician today are, we have people like these who have osteoporosis and are clearly at increased fracture risk. We also know that bisphosphonates decrease fracture risk, and do so substantially.

Some of the treatments now are inexpensive, so at least for some of the treatments that are available, the cost is not a stumbling block to treating people. But our problem is that the treatment goes for a long time, yet we don't know the optimal length of treatment. And what do we do about side effects? Who's going to get them? We obviously don't have enough data. And does concern for the side effects actually lead to decreased adherence to the drugs?

Well, there's one study that I've listed here from Australia suggesting that, yes, what's intuitively correct, that concern about the side effects is going to lead to decreased persistence with therapy. It actually has been demonstrated that this is so.

Well, is adherence important? And the answer to that is yes. And this is a study from Dr. Siris showing that patients need to take 75 to 80 percent of their bisphosphonate drugs in order to have a demonstrable decreased fracture risk.

Well, do we accomplish that? No. Most of the studies show that patients do not adhere to therapy for the necessary amount of time, and this is a major problem. Well, there are a lot of reasons for it. The cost was a problem and still is for some therapy; the fact that osteoporosis is asymptomatic until the patient fractures; the concern about adverse effects, and the complex dosing. After all, many of our patients are older. They have a large pill burden to begin with. And to tell them to take a pill separately from everything else on an empty stomach with a glass of water, and they can't take all their other pills at the same time, is a major stumbling block for some of our patients. And so it's clear that there are problems with adherence.

Well, what about the side effects? Well,

there are some that are relatively mild or avoidable. What about worsening of GERD or gastroesophageal reflux disease? Following orders is important. I see my patients in the Department of Veterans Affairs. My patients have all been in the military. They know how to follow orders. And, generally, they do quite well. When we see them back, we ask them specifically to tell us how they take their medication. That's very eye-opening sometimes, but it really helps to get that.

If the patients take the treatments, the oral treatments, properly, they're less likely to have problems. If they have GERD that's not under control, they're not good candidates to start their oral bisphosphonate right away. We try to get it under control. Of course, we're concerned about long-term use of proton pump inhibitors and inappropriate use of PPIs, but we certainly take that into account. We don't use oral therapy in those patients who already have esophageal mobility disorders, so we try to tailor our therapy to the given patient.

What about the acute phase reaction that's seen with intravenous bisphosphonates, usually with the first dose? Well, those patients need to be hydrated. We can treat them with acetaminophen. In addition to counseling each of the patients, I hand them a one-page instruction sheet and try to tell them how important it is to do those things. Most of the time, this is not a problem.

Hypocalcemia is unusual, but if you assure that the patient has adequate calcium and vitamin D intake and that their serum calcium to begin with is normal, then the chances of this are very small.

What about renal toxicity? Well, at the same time we measure their serum calcium, we measure their estimated glomerular filtration rate or another measure of renal function, and we make sure that we give the patients -- give those patients who have adequate renal function their bisphosphonate without concern about that. Those who have low renal function, we would not use it. So these side effects that I've listed here are general mild or avoidable.

Well, then, many of you have heard about atrial fibrillation, and I won't spend a lot of time on this except to say that the meta-analyses of atrial fibrillation as being a potential side effect have not been consistent. And I even found a recent study from Korea which suggested that bisphosphonates were actually protective for atrial fibrillation. So I don't think this is a big problem.

But we do have the problem of osteonecrosis of the jaw. We knew that it was a big problem in patients with cancer who are getting frequent doses of high-potency intravenous bisphosphonates. But in the patients who were getting osteoporosis doses, the frequency was much less.

When the ASBMR task force reviewed this, and that is referred to on this slide, their best estimate at that time was about 1 out of 10,000 to 1 out of 100,000 patients who are getting osteoporosis doses of bisphosphonate drugs. And at that time, the mechanism was still unclear. I think that's true today.

As a further disclosure, I was a member of a recent committee of the American Dental Association that has a new set of recommendations for osteonecrosis of the jaw that will be coming out in the Journal of the American Dental Association in November. And this is what this committee came to the unanimous conclusion of: that it's important for the physician to pay attention to the patient's teeth before starting treatment. We have been doing this routinely. Actually, at every visit, we have the patients open their mouths, and we take a look at their teeth, and we ask them about dental issues.

Not surprisingly, the ADA is for good dental hygiene for everyone, and suggests that, if possible, invasive dental procedures should be avoided. This is because many of the cases of osteonecrosis of the jaw have been found after people have had dental extractions or other major procedures. However, the ADA committee came to the conclusion that there was no need to stop treatment if the procedures were needed.

1 So, if possible, do the procedures before
2 starting bisphosphonate therapy; but if something
3 comes up while the patient is on bisphosphonate
4 therapy, there was no particular reason to stop
5 therapy because the risks were relatively low. And
6 the worst case scenario they thought was one out of
7 a thousand cases, probably fewer than that, but
8 that was the worst case. And, actually, the ADA
9 prefers the term "antiresorptive-associated
10 osteonecrosis of the jaw" because other
11 antiresorptive drugs may also be associated with
12 this particular side effect.
13 What about esophageal cancer and oral
14 bisphosphonates? Again, there were two studies
15 that came to different conclusions, interestingly
16 enough, from the same database. And a very nice
17 review of this was done by Dixon and Solomon that
18 I've listed here. And they came to the conclusion
19 that there probably was no increased risk in the
20 first three years of bisphosphonate therapy. But
21 at the worst, in years 4 to 7 of bisphosphonate
22 therapy, there might be five extra cases of

esophageal cancer per 10,000 patient-years.

But if you think about it, and think about the first patient that I presented to you today, who are the patients who get both esophageal cancer and osteoporosis? Well, they're older patients, those who take in alcohol to excess, and smokers. And so it's not surprising that we might see an association here. I don't think that the absolute number of patients who are going to be affected by this will be great.

We come to, then, the atypical subtrochanteric fractures. As mentioned, I was a member of the ASBMR task force on this. These are unusual. The mechanism is still unclear. And we do not know the background incidence because we don't know whether osteoporosis patients are at risk for atypical fractures in addition to typical fractures. The ICD-9 codes are not terribly helpful in determining the background incidence of these atypical fractures.

The task force came to the conclusion that there were probably 5 cases per 10,000 patient-

1 years; and from various reports, the estimation is
2 that bisphosphonate drugs save 30 to 100 typical
3 fractures for every atypical fracture that is
4 experienced.
5 Well, one of the problems with
6 bisphosphonates is their long half-life. One of my
7 colleagues says this is the gift that keeps on
8 giving. And the half-life has been estimated in
9 years, but there's another layer of complexity here
10 that I want to illustrate.
11 This is a recent study showing that women
12 who had been on osteoporosis bisphosphonates for
13 postmenopausal osteoporosis were discontinued for
14 14 months. Using HPLC, 41 percent of the women had
15 detectible alendronate in their urine. Those women
16 who had been on risedronate, though, none of the
17 women had detectable risedronate in their urine.
18 I'm going to show you just two brief slides
19 on risedronate. This is a study from Nelson Watts
20 showing that after three years of risedronate, and
21 then followed by one year of discontinuation, they
22 noted decreased bone density and increased bone

turnover markers; but the fracture risk at that one year was still less than the placebo group.

In a very recently released study of the longer-term extension of that trial, seven years of risedronate plus one year of discontinuation led to decrease in total hip and trochanter bone density, but stability in the femoral neck and spine, increase in bone turnover markers. But the numbers are so small that no fracture information can be derived from it.

The reason I bring this up is that it will be useful in comparing this with what Dr. Bauer is going to show you with alendronate. But what it means is that the specific bisphosphonate that the patient has taken plays a role. That's one more layer of complexity that the physician has to deal with when dealing with the patient sitting across from him or her.

So this is data that you don't see in the news. There are now four studies showing that bisphosphonates may lead to lower mortality. And the first study was the HORIZON trial, post hip

fracture trial, that showed that zoledronic acid not only led to fewer fractures compared to the placebo patients, but there was lower mortality in them as well. There's another study showing that oral bisphosphonates do the same thing, with a 63 percent relative risk per year of therapy in hip fracture patients who received oral bisphosphonates.

In the Dubbo trial from Australia, they could demonstrate decreased mortality in women on bisphosphonates, and probably so in men. And a recent study of institutionalized elders followed prospectively, there was also decreased mortality -- regardless of all the potential side effects, decreased mortality, the hardest outcome -- in those patients who took bisphosphonates.

So, in summary, we have patients today who are clearly at risk for fractures, and we know that bisphosphonates decrease fracture risk. Adherence is really important. There are a lot of things that keep our patients from persisting with their

therapy, and that's a problem. We need to monitor that.

We have to treat relatively asymptomatic patients for 5 to 10 years, but we don't know what the optimal length of treatment is. Despite rare side effects, those patients who take bisphosphonates have fewer fractures and lower mortality. These findings need to be shared with our patients, and the general public needs to know this as well.

Thank you very much for your attention.

[Applause.]

DR. CARSON: Thank you, Dr. Adler. We'll move on, and there will be some time for questions at the end of the FDA presentations.

Dr. Theresa Kehoe, who's the clinical team leader, will now present bisphosphonates and the regulatory history.

FDA Presentation - Theresa Kehoe

DR. KEHOE: Thank you, Dr. Adler. I am Theresa Kehoe, medical officer and clinical team leader in the Division of Reproductive and

Neurologic Products. You have heard the clinical challenges that face practitioners treating patients with osteoporosis, and I am now going to continue the discussion and provide an overview of the regulatory history of bisphosphonates.

Just as a reminder, we're talking here about bisphosphonates for the treatment of osteoporosis. Osteoporosis is a systemic skeletal disorder of compromised bone strength that predisposes an individual to an increased risk of fracture. Currently, an estimated 10 million people in the United States have osteoporosis, and an estimated 34 million people have low bone mass and are at risk for osteoporosis.

Bone mineral density is primarily used for diagnosis of osteoporosis. The World Health Organization classification criteria for osteoporosis by bone mineral density are outlined here. A T-score more positive than minus 1 is considered normal. Minus 1 to minus 2.5 is considered low bone mass, and more negative than minus 2.5 is considered osteoporosis.

In 2008, the World Health Organization released FRAX, which is a tool developed to evaluate fracture risk. The FRAX algorithm integrates both femoral neck bone density and other clinical risk factors. The results of FRAX are reported, as you heard from Dr. Adler, as the 10-year probability of hip fracture and the 10-year probability of major osteoporotic fractures.

Osteoporosis treatment guidelines are available, and those listed here are from the National Osteoporosis Foundation. In 1998, when guidelines were first released, treatment was recommended for patients with a bone mineral density T-score of less than minus 2, or less than minus 1.5 if other risk factors were present.

The newly released 2008 guidelines incorporate FRAX. The guidelines have evolved, and therefore now it is recommended that patients who have fractured should be treated as well as patients with a bone mineral density in the osteoporotic range. Patients over 50, using the FRAX calculator, with a 10-year probability of a

1 hip fracture of greater or equal to 3 percent, or a
2 10-year probability of major osteoporotic fracture
3 greater than 20 percent, should be treated.
4 Since 1994, in order for a drug to be
5 approved for treatment of osteoporosis, the sponsor
6 must demonstrate nonclinical evidence of bone
7 quality, including biomechanical testing of bone
8 strength. They must demonstrate fracture reduction
9 efficacy in a fracture trial. They must
10 demonstrate bone quality and normal bone
11 mineralization on bone biopsy in humans using bone
12 histomorphometry. And then once fracture efficacy
13 is established, subsequent indications and new dose
14 regimens can be based on bone mineral density
15 noninferiority.
16 Currently there are four bisphosphonate
17 products, all listed here, available for the
18 treatment of osteoporosis. The dosing regimens
19 range from daily oral dosing to once-yearly
20 intravenous dosing. And I would like the committee
21 to note that there is an error in table 1 of the
22 FDA briefing document. Boniva is listed by the

generic name risedronate. That is not correct. The generic name for Boniva is ibandronate.

We have heard a lot about bisphosphonates being the gift that keeps on giving. That is because bisphosphonates are pyrophosphate analogs and they bind to the hydroxyapatite crystals in bone and are incorporated into bone mineral. Once incorporated into the bone, the bisphosphonate remains until bone is resorbed by osteoclast activity. The osteoclast is responsible for bone breakdown in the normal bone life cycle. As the osteoclast breaks down bone, the bisphosphonate is released and causes the osteoclast cell death.

There's a long history of bisphosphonate drugs in the United States. The first approval occurred in 1977. That was etidronate, trade name Didronel, which was approved for treatment of Paget's disease of bone and heterotopic ossification. The first bisphosphonate approval for osteoporosis indications occurred in 1995, which was Fosamax, followed by Actonel in 2000, Boniva in 2003, and Reclast in 2007.

Fracture efficacy data is available for all bisphosphonates approved for osteoporosis. This slide outlines the efficacy achieved. In these trials, the proportion of subjects experiencing morphometric vertebral fractures is the primary endpoint. Morphometric vertebral fractures are generally asymptomatic fractures noted on X-ray. So I point this out to try to alleviate some confusion in what's being done in some of the discussions later on.

Clearly, this class of drugs is very effective in reducing these fractures, and the actual risk reductions range from 2 to 11 percent, with relative risk reductions ranging from 41 to 70 percent. We also know that these drugs are used by many patients. Represented in this slide are the drug use data for bisphosphonates. From 2005 to 2009, 4 and a half to 5 million patients over age 55 filled a prescription for a bisphosphonate in the outpatient retail pharmacy setting. Most of these prescriptions were for women.

So we know that bisphosphonates have robust

efficacy and are prescribed to millions of patients. Does this translate into the population level? In 2010, in a study by Nieves using the National Hospital Discharge Survey, we can see that in 1996, one year after the first approval of bisphosphonate for osteoporosis, the discharge rate for hip fracture was 598 per 100,000 patients. In 2006, the rate has fallen to 428 per 100,000 patients. This occurred at a time when the population is aging, and we recognize that age is a major risk factor for fracture. Therefore, despite the increasing age of the population, hospital discharge rates for hip fracture has fallen. Treatment with bisphosphonates may play a role in this finding.

A significant part of our jobs as regulators is to label a drug with regard to the expected benefits and the expected risks. When we talk about the risks, safety assessment is an ongoing process. Now we're going to focus on those major safety events that have been seen with bisphosphonates.

Because of their action as antiresorptive agents, bisphosphonates are well-recognized to exacerbate hypocalcemia. Bone is the largest reservoir of calcium in the body, and bisphosphonates effectively shut off that reservoir. Therefore, at the initial approval for all of the bisphosphonate drugs, there is a contraindication for patients with preexisting hypocalcemia and a warning and precaution for other patients who may be at risk.

Reports of hypercalcemia adverse events in the clinical trials were low, and that is mainly because all patients received calcium and vitamin D in these trials. However, hypocalcemic tetany attributed to bisphosphonates has been reported in the outpatient setting.

Oral bisphosphonates are well-known to cause gastrointestinal esophageal adverse reactions. This is attributed to mucosal irritation mainly of the esophagus. These findings were initially labeled as a precaution at the time of Fosamax approval in 1995 and then upgraded to a

1 contraindication and a warning in 1997. Product
2 labeling has continued to be updated over the
3 years, with the last update occurring in 2009. At
4 that time, the gastrointestinal adverse events
5 warning and precaution for all oral bisphosphonates
6 were aligned as class labeling.
7 This slide shows the contraindication for
8 gastrointestinal adverse reactions, namely,
9 abnormalities of the esophagus which delay
10 esophageal emptying, and also the inability to
11 comply with dosing instructions that require an
12 individual to stand or sit upright for 30 minutes
13 or, in the case of Boniva, 60 minutes.
14 The next two slides show the current warning
15 and precaution related to gastrointestinal adverse
16 events. It is quite detailed, outlining that oral
17 bisphosphonates may cause local irritation of the
18 upper gastrointestinal mucosa, and that caution
19 should be used when the drug is given to patients
20 with active upper gastrointestinal disease.
21 It also reminds physicians to be alert for
22 any signs or symptoms signaling a possible

esophageal reaction, and to instruct patients to discontinue the drug and seek medical attention if they develop dysphagia, odynaphagia, retrosternal pain, or newer or worsening heartburn.

We know that not following dosing instructions is associated with a greater risk of these gastroesophageal adverse reactions, so the labeling does recommend that it is important that the full dosing instructions are provided to and understood by the patient.

In the postmarketing period, bone, joint, and muscle pain has been reported with bisphosphonate use. The etiology of pain is not clear. There does not appear to be a temporal relationship to the drug administration. Initially, these findings were labeled as postmarketing adverse reactions. However, with continued reports of severe reactions, it was upgraded to a warning and precaution in 2004.

Concerns regarding renal toxicity emerged during the zoledronic acid oncology program under the trade name Zometa. The risk was seen to be

dose-dependent, and the risk was also increased with a more rapid infusion time. Both 5-minute and 15-minute infusions were evaluated in the clinical program. Therefore, the approved dosing instructions were an infusion no less than 15 minutes.

Zoledronic acid, under the trade name Zometa, was approved for oncology indications in 2002. Reclast, also zoledronic acid, was approved in 2007 for osteoporosis indications. At the time of approval, product labeling contained a warning and precaution for renal impairment, and the same dosing instructions used in Zometa were also used in Reclast, that is, an infusion of no less than 15 minutes.

Postmarketing adverse events of renal failure have been reported. Some patients required dialysis, and some had a fatal outcome. The original Reclast warning and precaution was updated in March 2009. However, reports have continued, so the warning and precaution was updated again and a new contraindication was added for patients with a

creatinine clearance less than 35 and with evidence of acute renal impairment. And this was added last month.

Osteonecrosis of the jaw is a clinical entity that was known to occur in patients with head and neck irradiation for cancer therapy. Following the approval of Zometa in 2002, osteonecrosis of the jaw was noted in cancer patients who had no head or neck irradiation but who had been exposed to IV zoledronic acid or IV pamidronate. An Oncology Drugs Advisory Committee meeting was held on this topic in March of 2005, and a warning and precaution regarding osteonecrosis of the jaw was added to the oncology product labels in 2005.

Although ONJ was first seen in the oncology population, there was also concern regarding ONJ risk in the osteoporosis population. For this reason, a warning and precaution was also added to the osteoporosis drug labels in 2005. You will hear more about osteonecrosis of the jaw in Dr. Kuyateh's presentation.

FDA began receiving reports of the subtrochanteric hip fractures in 2008. Subtrochanteric fractures are known to occur mainly in two populations, young patients with high energy trauma and elderly patients with minor trauma. A review of the bisphosphonate clinical trial data was conducted, and we found a total of 19 subtrochanteric fractures had been reported. However, it became clear during our review that the features of the fractures being reported were not typical.

In October 2010, the American Society for Bone and Mineral Research task force presented their definition of atypical subtrochanteric fractures. The major features of these fractures include the location, which is anywhere along the femur between the lesser trochanter and the supracondylar flare. There is minimal or no trauma involved, the fractures tend to be transverse, and they are not comminuted. The fractures can be complete, where both cortices are involved, and may have a medial spike, or incomplete, which usually

1 involves the latter cortex only.
2 To present a visual of these fractures we
3 are talking about, in the middle is a normal femur.
4 On the right -- let's see if I can do this; maybe
5 not. On the right is a transverse fracture from a
6 patient on bisphosphonates, and it does have most
7 of the features mentioned in the ASBMR guidelines.
8 However, on the left we see an almost identical
9 fracture that occurred in a 90-year-old patient
10 with osteoporosis who had never seen a
11 bisphosphonate.
12 Although the data is still accumulating, we
13 were very concerned regarding these fractures. And
14 because there is an opportunity to intervene, a
15 warning and precaution was added to the product
16 labels in January of this year. The warning
17 outlines that fractures have been reported in
18 patients who are treated with bisphosphonates, and
19 that causality has not been clearly determined. It
20 also points out, most importantly, that the
21 fractures may be bilateral and that patients may
22 have a prodromal pain syndrome. It also recommends

that patients with a history of bisphosphonate exposure who present with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete fracture. Again, you will hear more about atypical subtrochanteric fractures in Dr. Kuyateh's presentation.

Not all adverse events noted in the clinical trials or in the postmarketing period require warning and precaution language in the product labels. Some of these you have heard about from Dr. Adler. As you heard from Dr. Adler, an imbalance in the incidence of serious atrial fibrillation events was noted in the Reclast clinical trials.

Based on these concerns, FDA requested placebo-controlled clinical trial data from all bisphosphonate sponsors, and a thorough review was conducted. Across all studies, there was no clear association between overall bisphosphonate exposure and the rate of serious or nonserious atrial fibrillation events. Therefore, atrial

fibrillation was labeled as an adverse reaction in the Reclast product labeling, but class labeling was not sought.

So what we know is that bisphosphonates are highly efficacious in reducing the risk of fractures and are widely prescribed for the prevention and treatment of osteoporosis. We are very concerned about the recent safety events and the question of the risks and benefits of long-term use of these drugs. Because of these concerns, language was added to the bisphosphonate product labeling in January of this year.

In the indications and use section of the product label, an important limitation of use statement was added, and that is that the safety and effectiveness of the drug for the treatment of osteoporosis, based on clinical trial data of however many years duration, the optimal duration of use has not been determined, and all patients on bisphosphonate therapy should have the need for continued therapy reevaluated on a periodic basis.

We have continued to evaluate all available

data concerning the questions of the duration of use for bisphosphonates. This is the topic and the focus of the rest of the FDA presentation this morning. Both long-term safety and long-term efficacy will be discussed. Long-term safety is derived mainly from epidemiologic studies, and long-term efficacy is derived from the available clinical trial data, with a focus specifically on those patients who had long-term bisphosphonate exposure.

Now I'd like to turn the podium over to Dr. Fatmatta Kuyateh, from the Office of Surveillance and Epidemiology, who will continue FDA's presentation with an in-depth review of the safety events under discussion. Thank you.

[Applause.]

FDA Presentation - Fatmatta Kuyateh

DR. KUYATEH: Thank you, Dr. Kehoe.

Good morning. My name is Fatmatta Kuyateh. On behalf of the Office of Surveillance and Epidemiology, I will be presenting findings and conclusions from a safety review that was conducted

pertaining to long-term use of bisphosphonates indicated in the prevention and treatment of osteoporosis.

First, I will give a summary of findings from a duration of use analysis that we conducted. Then I'll give a very brief overview of the safety issues of concern with long-term use of bisphosphonates. I'll touch on the utility of FDA AERS data in characterizing the risk of these safety issues to bisphosphonate use. Finally, I'll give a more detailed account of our epidemiology review, and close with our overall conclusions.

To better put into context the evidence concerning the safety issues with long-term use of bisphosphonates, we conducted a duration of use analysis using a data set compiled from the SDI Vector One database. The data set included patients with IV and oral prescriptions dispensed from retail pharmacies between the years 2005 to 2010. We restricted these analyses to incident users. Our total sample size was about 369,000, of whom more than two-thirds were older than 60 years.

Please note that this sample and the results that follow are not nationally projected.

We observed that patients receiving long-term bisphosphonate therapy represent a minority of the sample. This graph shows data for all patients in the sample, with months of therapy on the Y axis and percent of total patients on the X axis. Approximately 9 percent of the sample continued therapy for three or more years, and 0.74 percent for five years or more.

Not shown on this graph is the observation that in patients older than 60 years, 10 percent continued bisphosphonate therapy for more than three years and 2 percent for more than five years. Although only a minority of the sample used the drugs long term, given the widespread use of bisphosphonates, as you heard earlier from Dr. Kehoe, the actual number using them long term could still be fairly large.

These findings are not very different from those of published studies. Our study has some key advantages. We used the pharmacy-based claims

1 database, which includes all payors, our study is
2 larger than other published studies by an order of
3 magnitude, and we focused only on bisphosphonates
4 indicated in the treatment and prevention of
5 osteoporosis.
6 Our study does have some limitations,
7 however. The data, as mentioned earlier, are not
8 nationally projected, and we do not have enrollment
9 data for the patients for whom these drugs are
10 prescribed. So incident users were defined using
11 algorithms based on dispensing history.
12 Now, I'll present a brief overview of the
13 safety issues. Cases have been published since the
14 year 2005 of unusual femoral fractures associated
15 with bisphosphonate use. These fractures have
16 since been designated as atypical femoral
17 fractures. Different reports and studies have used
18 different elements to define atypical fractures,
19 and this has made it difficult to estimate the
20 incidence of these fractures in the general
21 population.
22 As you heard earlier from Dr. Kehoe, the

American Society for Bone and Mineral Research, or ASBMR, developed the case definition for this outcome with required elements including occurrence between the lesser trochanter of the femur and supracondylar flare, minimal or no trauma associated with the fracture, a specific configuration, usually transverse, noncomminuted, and involvement of both cortices or only the lateral cortex. Other findings such as beaking, generalized cortical thickness, and prodromal pain are not required.

Cases of osteonecrosis of the jaw, or ONJ, were first reported in 2003 with intravenous formulations of bisphosphonates. The incidence of ONJ in cancer patients who receive IV bisphosphonates for management of skeletal lesions is estimated to be 1 to 5 percent. The background incidence of ONJ is unknown, and the true incidence among patients who use oral bisphosphonates has yet to be determined.

In 2007, a task force of the American Association of Oral and Maxillofacial Surgeons

1 developed a case definition of bisphosphonate-
2 related ONJ which required greater than eight weeks
3 of exposed bone and no history of radiation to the
4 jaws, in addition to bisphosphonate exposure.
5 Esophagitis and esophageal ulcer are well-
6 known and labeled adverse events of oral
7 bisphosphonates. But more recently, concerns of
8 esophageal cancer have surfaced, especially
9 following a report in the year 2009 of 23 cases
10 that occurred in the U.S. between 1995 and 2008.
11 Esophageal cancer is rare in the general
12 population, with an estimated age-adjusted
13 incidence of 3 to 6 cases per 100,000 population in
14 2008. The true incidence among bisphosphonate
15 users is unknown.
16 I'll go into more details about the safety
17 issues, but first I'd like to address the utility
18 of FDA Adverse Event Reporting System data in
19 assessing the association of these outcomes to
20 long-term bisphosphonate use.
21 The FDA receives postmarketing adverse event
22 reports into AERS, a computerized passive

surveillance system, from industry, consumers, and healthcare professionals. Of note, because AERS data are spontaneous data, one cannot calculate incidence rates of adverse events. FDA has received reports of atypical fracture, ONJ, and esophageal cancer following bisphosphonate exposure, which has led to further investigation.

However, in general, there are some major limitations when interpreting AERS data concerning the bisphosphonate adverse events. One such limitation is that reports generally lack clinical information meeting case definitions, and another limitation is that information on duration of exposure is absent or frequently uncertain.

In addition, because of the relatively long latency of some of the outcomes of interest, reports are less likely to be attributed to exposures that may have occurred years earlier. Therefore, overall, FDA was unable to characterize the association of adverse event outcomes to bisphosphonate exposure using AERS data.

In light of these limitations, we set out to

conduct a review of the epidemiological data. In summary, here are our findings. We found that femoral fractures demonstrating radiographic features specified in the ASBMR case definition of atypical fractures were associated with bisphosphonate use, but the relationship to duration of use was unclear, as was causation. We found the prevalence of ONJ may increase with increased duration of exposure to oral bisphosphonates, but, again, causation could not be established. We also found that evidence regarding esophageal cancer and bisphosphonates is, at the moment, inconclusive.

You heard a brief overview of the long-term safety issues a few slides ago. Now I'll give more details about our review of the epidemiologic evidence, and I'll start off with atypical femoral fractures.

We conducted a literature review of studies on the risk of atypical femoral fractures with use of bisphosphonates. We searched for all bisphosphonates approved in the U.S. for the

prevention and treatment of osteoporosis, including alendronate, zoledronic acid, ibandronate, and risedronate. In addition, we used keywords indicative of femoral of subtrochanteric fracture. Published randomized clinical trials, or secondary analyses thereof, and observational studies were reviewed for relevance. Case reports and case series were excluded. Our final review included 10 studies, which I'll show you in the slides that follow.

This table summarizes the studies from our final review that did not find an association of atypical femoral fractures with use of bisphosphonates. I have concealed the rest of the results and will show them to you in succession as each study is being discussed. Of note, the term "atypical femoral fracture" varies from one study to the next.

Abrahamsen and others conducted a cohort study using the Danish National Registry data and found no association of low energy, subtrochanteric, or femoral shaft fractures with

bisphosphonates, even after six years of use. A strength of the study is that they included patients with previous fracture and matched on site of that previous fracture, thus somewhat controlling for baseline differences in risk.

In this study, glucocorticoid use was noted to be higher in patients with atypical fractures, suggesting that glucocorticoid use could contribute to the outcome. But because it was adjusted for in the models rather than reporting outcomes by strata, this could not be confirmed. Another limitation to this and other studies using diagnostic codes is that the codes do not distinguish between spiral fractures and transverse femur fractures.

Kim and colleagues' cohort study compared osteoporotic patients treated with bisphosphonates to those treated with raloxifene or calcitonin, and found no association of subtrochanteric or femoral shaft fractures to bisphosphonates, even after five years of use. However, the number of cases is low.

Another large cohort study by Vestergaard

and colleagues compared bisphosphonate users for the treatment of osteoporosis to matched controls from the general population. They found an increased risk of subtrochanteric and femoral shaft fracture with bisphosphonate use, but also observed an increased odds before initiation of therapy.

None of the three cohort studies just described reviewed radiographs or radiographic reports.

Black did a secondary analysis of data from three original randomized controlled trials, and was the only one of these studies listed in this table to assess radiographic reports for atypical features. The single most important limitation of this analysis, however, is the very small number of events and the fairly wide confidence intervals, suggestive of decreased power. In addition, two of the trials lasted no more than 4 and a half years. Thus, long-term use could not be assessed.

This table shows a summary of studies that found an increased risk of femoral fractures with bisphosphonate use. Abrahamsen and others

conducted another study using the Danish National Registry. Contrary to their 2009 study, this study found an increased risk of atypical fractures with bisphosphonate use. They evaluated dose response and duration, but found no significant differences in subtrochanteric and femoral shaft fracture rate with increasing dose.

Of note, this study was much larger and had more power than the previous study. This study's strengths lie in the fact that they evaluated dose response and had increased power with a 4 to 1 matching system. However, they did not assess radiographs or radiographic records to confirm atypical status.

Both Giusti and Lenart's case-control studies compared bisphosphonate use among femoral shaft cases with atypical radiographic features to femoral shaft controls without those features, although the fracture definitions were slightly different across the two studies.

Giusti found an increased risk of atypical fracture with bisphosphonate use, but no

significant difference in mean duration of use between the two groups. The key strength of the Giusti study is that there was blinded review of all actual radiographs. However, the number of cases was very low and the confidence interval was wide, raising questions about the precision of these findings.

Lenart also found an association between atypical features and bisphosphonate use. Like the Giusti study, this study also used actual radiographs; but again, the numbers were too low to allow for further characterization of the association.

The Wang study was one of trends that observed an increase in bisphosphonate use over an 11-year period which preceded an increase in proportion of hip fractures that were subtrochanteric. They concluded that this adjusted in association, although this conclusion is limited by the ecologic nature of the study that may not have allowed for assessment of other contributing factors.

This table shows studies that observed an association of fracture to duration of bisphosphonate use, although they are in disagreement as to how much cumulative use is harmful with respect to the outcome of interest.

Park-Wyllie and others conducted a nested case-control study in a cohort of Ontario women who had initiated oral bisphosphonate therapy within a given period of time. The study compared duration of bisphosphonate use between cases hospitalized with subtrochanteric or femoral shaft fracture and controls matched on age and cohort entry.

The investigators observed that extended use of bisphosphonates for five years or longer was associated with an increased risk of hospitalization for subtrochanteric or femoral shaft fracture, while intermediate use of three to five years was not. They also observed that approximately 1 out of every 10 subtrochanteric or femoral shaft fractures in the population was attributable to extended bisphosphonate use of five or more years.

This study had by far the largest number of cases, implying increased power. However, radiographs were not evaluated for the cases. This study was also restricted to women aged 68 years and older, raising concerns about the generalizability to all bisphosphonate users.

Schilcher and others published a case-control study that compared bisphosphonate use and duration among cases of atypical fractures defined by radiographic findings to bisphosphonate use and duration in controls with fractures that did not have atypical features. They observed that the risk of atypical fracture was higher with bisphosphonate use, as short as one year, and progressively increased with increased duration. They also observed a 70 percent reduction in the risk for every year since the last use, regardless of how long bisphosphonates had been used for.

Similar to the Giusti and Lenart studies, this study reviewed actual radiographs to designate atypical status. One possible reason for the differences between these two studies is that the

Schilcher study defines cumulative use by excluding all periods of non-use. Thus, one year of use in this study may not be equivalent to one year of use in the Park-Wyllie study.

Of note, the observational studies just reviewed vary as to which potential confounders were measured and adjusted for, and residual confounding is likely an issue for most of them.

To summarize the atypical fracture data, there is mixed evidence concerning the risk of femoral fractures with bisphosphonate use. And because of individual strengths and weaknesses of each study, some of which have been described for you here today, it is difficult to select any one study as the definitive, most accurate study. There does, however, appear to be some association of atypical radiographic findings, as defined by the ASBMR, to bisphosphonate use, although causality is uncertain and relationship to duration of use is unclear.

Now we'll take a look at some of the evidence regarding ONJ and oral bisphosphonates.

Previous studies of ONJ have focused on IV bisphosphonates in a setting of multiple myeloma breast cancer and other malignant disease, where the risk of ONJ may be confounded by the disease being treated. One exception is a cohort study by Cartsos and others that found an elevated risk of inflammatory necrosis of the jaw. This outcome, however, is designated by an ICD-9 code different from that for ONJ.

Studies done before an ICD-9 code for ONJ was established faced challenges in identifying cases of ONJ using medical claims data. In addition, many of the studies that have identified risk factors for ONJ have been small case series or prevalent studies not designed to determine the risk of ONJ associated with bisphosphonates.

One such prevalent study by Mavrokokki and others estimated that 1 in about 8400 patients treated with oral bisphosphonates for osteoporosis developed ONJ. This study estimated the prevalence of ONJ by dividing the number of cases identified from the survey by the number of patients receiving

1 oral bisphosphonates for osteoporosis, which was in
2 turn estimated from the number of total
3 prescriptions.
4 In 2006, FDA contracted with Kaiser
5 Permanente in northern California to conduct the
6 PROBE study. The objective of this cross-sectional
7 study was to determine the prevalence of and risk
8 factors for ONJ among patients with chronic oral
9 bisphosphonate exposure.
10 Because ICD-9 coding for ONJ was not
11 available at the time, a dental symptom survey was
12 mailed out to patients inquiring about symptoms
13 associated with ONJ. Active members within the
14 Oakland, Santa Clara, and Sacramento areas, age 21
15 to 90, who had received at least one year of oral
16 bisphosphonates were included. Patients with any
17 IV bisphosphonate use and those with a history of
18 oral cancer were excluded.
19 In summary, we found 9 cases of ONJ, and
20 this amounted to a prevalence of 0.1 percent among
21 respondents, or 28 cases per 100,000 person-years
22 of exposure.

This graph shows the prevalence of ONJ among all respondents by years of bisphosphonate use. Prevalence of ONJ was 0.21 percent among those with four or more years of use versus 0.04 percent among those with less than four years of use. Of note, the median duration of use among these 9 cases was 4.4 years. Among 2100 respondents with less than 2.5 years of bisphosphonate treatment, there were no ONJ cases.

Multivariable logistic regression models adjusting for age and history of rheumatoid arthritis showed that odds of ONJ was elevated with bisphosphonate treatment duration greater than or equal to four years, but the finding was not statistically significant.

In conclusion, evidence from the PROBE study is suggestive of an increased prevalence of ONJ among those exposed to oral bisphosphonates long-term, with highest prevalence occurring after four or more years. But interpretation of these results is limited because we cannot infer causality, we can't infer incidence, and the number of actual ONJ

cases was very small.

Finally, we'll take a look at the evidence concerned esophageal cancer and long-term use of bisphosphonates.

We reviewed the two large studies that Dr. Adler had mentioned earlier. One, a cohort study, and one a case-control study were conducted using the same large U.K. database. The cohort study did not find an association of bisphosphonate use to esophageal cancer or esophageal and gastric cancer combined. However, the case-control study, which overlapped in time period with the first study and possibly included patients from that study, found a 30 percent increased risk of esophageal cancer among bisphosphonate users. That risk increased to 93 percent with cumulative use of 10 or more prescriptions.

The differences in results could be due to differences in study design. The case-control study stratified on confounders, while the cohort study adjusted for confounders in the model, and models could have adjusted away any potential

confounders in the causal pathway. On the other hand, the case-control study had increased power with the 1 case to 4 control matching design. Case definitions may not be comparable across the two studies. The cohort study required consistent recording of codes, although the exact details were not made available.

Two other studies, one of them restricted to patients with Barrett's esophagus, did not find an association of oral bisphosphonates to esophageal cancer, while another study found a decreased risk among bisphosphonate users compared to non-users. Due to limited access to histology, none of the studies could differentiate between adenocarcinoma and squamous cell carcinoma, which have different sets of risk factors.

In summary, the epidemiologic evidence available regarding any possible association between esophageal cancer and bisphosphonates is inconclusive due to a number of factors, including conflicting results within the same database in similar time periods, case definition variation and

uncertainty regarding accurate capture of diagnosis, and unclear role of potential confounding factors such as esophagitis and Barrett's esophagus.

Our overall conclusions are as follows. AERS data cannot be used to assess the long-term safety issues of concern, but upon conducting a review of the epidemiologic data, OSE observed the following.

Atypical subtrochanteric and femoral shaft fractures with radiographic features consistent with the ASBMR case definition appear to be associated with bisphosphonates used in the treatment of osteoporosis, but we remain uncertain about causality and the relationship with duration of use.

ONJ may be associated with increased cumulative exposure to oral bisphosphonates, but causation could not be determined. And evidence concerning the association of esophageal cancer to bisphosphonates is inconclusive.

Dr. Whitaker will now discuss the long-term

efficacy data regarding bisphosphonates used for treatment and prevention of osteoporosis. Thank you for your attention.

[Applause.]

FDA Presentation - Marcea Whitaker

DR. WHITAKER: Thank you, Dr. Kuyateh.

Good morning. My name is Marcea Whitaker, and I will be presenting the efficacy data on the long-term use of bisphosphonates.

In response to an FDA information request, we received long-term data from the four bisphosphonate products used in the treatment of osteoporosis: Fosamax, Actonel, Reclast, and Boniva. We were interested in studies that met the following criteria: A duration greater than three years and a systemic and complete capture of fracture data, including the morphometric vertebral fractures and all clinical fractures, and those that included a useful comparator group.

Long-term data fulfilling these criteria are available from all of the bisphosphonates except for Boniva. The required Boniva fracture trial was

a three-year study and did not include an extension period, and therefore did not meet our criteria.

Two other studies supporting the approval of different Boniva formulations provided five years of continuous exposure and were composed of a two-year core study and a three-year extension phase. BMD was the primary endpoint, but vertebral X-rays for fracture assessment were not performed. Since fracture capture was incomplete, these two longer-term studies also did not meet our criteria.

The data used in the remainder of the presentation focused on the first three drug products. However, I will add that the five-year BMD data from Boniva are consistent with what will be presented for the bisphosphonate class.

The studies differed in design, the timing of assessments, and duration, with maximum exposure ranging from 6 to 10 years. However, all studies included calcium and vitamin D supplementation.

As a brief overview of the trial design, here's a schematic comparing Fosamax and Reclast, which were the most similar in design. Both had an

1 initial core study comparing active drug to
2 placebo. Both studies also had a randomized
3 withdrawal phase, denoted by the arrows, where a
4 subset of those patients treated with active drug
5 were then re-randomized to continue drug or they
6 were switched to placebo. The periods highlighted
7 in red in this slide and in the next illustrate
8 those data used for the BMD and fracture analyses
9 that will be presented.
10 Actonel also had an initial core study
11 comparing active drug to placebo, but also had four
12 extension studies through year 10. Continuous
13 risedronate therapy was only captured through
14 year 7, and the placebo group was maintained
15 through year 5, and then all subjects received open
16 label risedronate. A prospectively planned one-
17 year drug holiday period, followed by resumption of
18 treatment, occurred in years 8 to 10 for some
19 patients.
20 While we are fortunate to have long-term
21 data, we do acknowledge the following limitations.
22 Our analyses are post hoc and therefore were not

prespecified. Our data also focused on the subset of patients on continuous therapy. Since the primary endpoint for the extension studies was BMD, the studies were not powered for fracture.

The patients in the extension subgroups tended to have had fewer fractures and had greater increases in BMD during the core studies compared to their non-extension counterparts, representing some selection bias. The sample sizes are relatively small.

As the long-term extension studies progressed, there were fewer subjects in each time period. As a result, in addition to looking at the individual study data, we also performed a pooled analysis for fractures, combining data from the three drug products.

Finally, the timing of vertebral X-rays to assess morphometric fractures varied between the studies. X-ray assessment occurred at yearly intervals in the core studies, but only every one and a half to three years in the extensions. This required the lumping of fractures from concurrent

1 years. As a result, fracture rates from year to
2 year are not available, and the number of years
3 lumped into each category also varies. Despite
4 these limitations, the data were useful in
5 exploring trends following long-term bisphosphonate
6 use.
7 For each drug product, I'm going to start by
8 looking at the BMD results, which were the primary
9 endpoints for the extension studies.
10 The long-term Fosamax data included the FIT
11 and the FLEX treatment periods. FIT, which stands
12 for the fracture intervention trial, was made up of
13 two cohorts. Cohort 1 was a three-year study,
14 enrolling 2,000 postmenopausal women with vertebral
15 fractures at baseline. These subjects were also
16 enrolled into a one-year open label study. And
17 cohort 2 was the four-year study that enrolled 4400
18 postmenopausal women without vertebral fractures.
19 The mean age of both cohorts was 71 years, and the
20 subjects had a femoral neck T-score less than or
21 equal to a minus 1.6.
22 Patients in FIT were randomized to either

alendronate 5 milligrams or placebo. The FIT study was ongoing at the time when alendronate was approved, so at month 24, all the subjects in the alendronate 5-milligram group were increased to the approved 10-milligram dose for the treatment of osteoporosis.

At the start of FLEX, also known as the FIT long-term extension, 1,099 subjects who previously received alendronate in FIT, either from cohort 1 or cohort 2, were re-randomized into the three dose groups -- either alendronate 10, alendronate 5, or placebo -- for an additional five years. Note that there is an interval period between the end of FIT and the start of FLEX, which ranged anywhere from zero to two years. During this period, subjects were directed to continue alendronate.

So, overall, subjects received anywhere from three to six years of total alendronate therapy prior to entering FLEX, with the majority of subjects receiving five years of therapy. Subjects with greater than 10 years of exposure either had a long post-FIT period or had extended therapy at the

end of FLEX. As a result, it is more accurate to refer to the five years of FLEX as years 0 to 5 rather than years 5 to 10, although the years run concurrently for the majority of subjects. Before looking at the FLEX long-term results, I want to show the BMD data from the FIT three- and four-year studies.

BMD results are shown for the two cohorts, cohort 1, those with a baseline vertebral fracture, and cohort 2, those without. The graphs show the mean percent change in BMD from baseline over time for each cohort, either at the femoral neck or at the lumbar spine.

At the femoral neck, those taking alendronate in both cohorts had an increase in BMD of about 4 percent, while those taking placebo had decreases below baseline. At the lumbar spine, there were greater increases in BMD of about 6 to 7 percent, with some increases in the placebo group. The alendronate curves in the femoral neck as well as in the lumbar spine represent the same FIT time period, as will be seen on the next slide.

The long-term data for the years of FIT and FLEX are shown here, and focuses only on those 1,099 patients who completed FIT and then entered FLEX. The color code represents the re-randomized groups of alendronate 10, alendronate 5, and placebo. Recall that all FLEX subjects received alendronate during FIT. Therefore, the FIT part of both graphs are similar to each other, and also are similar to what was seen on the prior slide.

After re-randomization, the mean percent change from baseline at the femoral neck shows a plateau effect for those continuing on active therapy, either the 5 or the 10 milligrams, while those in the placebo group had an initial decrease in BMD over the first two years of about 2 percent, and then you see a plateau. And this plateau still is above the FIT baseline levels. At the lumbar spine, BMD continued to increase in all groups, but to a lesser extent in those re-randomized to placebo.

These results appear to indicate that there is maintenance of BMD at the femoral neck and

1 continued BMD increases at the lumbar spine for
2 active therapy, but also that BMD effects persist
3 after active drug is discontinued.
4 Recall that Actonel or risedronate data
5 included an initial three-year core period,
6 followed by the four extension studies. Patients
7 were randomized to risedronate 5 milligrams or
8 placebo for the first five years. All subjects in
9 years 6 to 7 were treated with open label
10 risedronate, and there's also a drug holiday period
11 that will be discussed in detail later. But
12 continuous risedronate data are only available up
13 to year 7.
14 The core study was one of the two
15 registration trials for Actonel and enrolled about
16 1200 postmenopausal women with multiple vertebral
17 fractures at baseline, with a mean T-score of a
18 minus 2.7, and the mean age was 70 years. However,
19 at year 6 to 7, there were only 164 patients
20 remaining, with only 83 of them on continuous
21 risedronate for the entire time.
22 These graphs show the change in BMD for

1 those patients enrolled in the seven-year Actonel
2 study. Those taking risedronate for the entire
3 time are shown on top in black, and the placebo
4 group is in red. And recall that all subjects
5 received open label in the years 6 to 7.
6 As seen with alendronate, those taking
7 continuous risedronate had maintenance of BMD at
8 the femoral neck and increases at the lumbar spine.
9 The placebo portion is similar to what was seen for
10 the FIT 3- and 4-year studies, with a decrease in
11 placebo in BMD at the femoral neck and increases at
12 the lumbar spine. The increases in years 6 to 7 in
13 the placebo group are attributed to those patients
14 who then were taking active risedronate therapy.
15 Reclast or zoledronic acid long-term data
16 includes six years of continuous exposure. The
17 Reclast core study was a 3-year registration trial
18 that enrolled about 7700 postmenopausal women with
19 either vertebral fractures at baseline or those who
20 had an osteoporotic range T-score with or without a
21 vertebral fracture. The mean age was 73 years.
22 Patients were initially randomized to receive

1 zoledronic acid 5 milligrams or placebo.
2 The three-year extension study enrolled 1233
3 patients who had received zoledronic acid in the
4 core study, and then re-randomized them to
5 continued zoledronic acid or placebo.
6 The BMD results for Reclast are similar to
7 what has already been described for Fosamax and for
8 Actonel, and the analysis only includes those
9 patients enrolled in both the core as well as the
10 extension studies. Recall that all subjects were
11 taking active therapy in the core study; therefore,
12 the first parts of each of the graphs are similar
13 between treatment groups.
14 At the femoral neck, after re-randomization,
15 the mean percent change from baseline plateaus in
16 active therapy, while there is a trend in those re-
17 randomized to placebo. At the lumbar spine, for a
18 subset of patients, there was continued BMD benefit
19 in all groups, but to a lesser extent in those re-
20 randomized to placebo.
21 So to summarize the BMD results across the
22 bisphosphonate drug class, continued therapy for

zero to five years resulted in a similar BMD response for all bisphosphonate products. Continued drug therapy beyond five years showed maintenance of BMD at the femoral neck and increases at the lumbar spine.

After three to five years of therapy, those that stopped active drug had a decreasing trend in BMD, with a plateau that remained above baseline levels at the femoral neck and continued increases at the lumbar spine. It is unclear these increases at the lumbar spine are drug-related or the result of artifact due to arthritic changes in the spine that increased BMD in patients over 60. These data suggest that continued therapy results in maintenance of BMD, but also there is residual benefit after drug is discontinued. But the true direction of this residual benefit is unknown.

Now we're going to move to the fracture results.

New vertebral fractures were the primary endpoints during FIT. During FLEX, however, the primary endpoint was BMD and the study was not

powered for fracture, although fractures were captured at safety endpoints.

During FLEX, the sponsor reported a 55 percent risk reduction only in clinical vertebral fractures using the pooled treatment group. An FDA analysis of the sponsor's vertebral fracture data are shown here. The rates represent the number of subjects from FLEX with at least one vertebral fracture during the extension study by treatment group. The vertebral fractures are broken down into three categories: the any vertebral fracture, the clinical vertebral fracture, or the morphometric vertebral fractures.

In the sponsor's data set, each new vertebral fracture was designated as either clinical or morphometric. Because some patients experienced both clinical and morphometric fractures, these subjects would only be counted once, in the "any" column, and therefore these numbers are lower than the sum of the two subtype columns.

As seen in the sponsor's analysis, fracture

benefit was only seen in the clinical vertebral fractures in both active treatment groups, with a calculated relative risk reduction of 61 percent. No benefit was seen for morphometric fractures nor for any vertebral fracture.

In addition to looking at vertebral fracture, we also looked at all osteoporotic fractures for those subjects who enrolled in both FIT and FLEX. Here and for all the fracture analyses, all osteoporotic fractures are defined as morphometric vertebral fractures and clinical osteoporotic fractures, excluding fractures of the fingers, toes, skull, and face. All subjects received alendronate during FIT, and then were re-randomized to the continued therapy with alendronate 10, alendronate 5, or placebo. For this table and for all subsequent fracture tables, the values represent the percentage of patients having at least one osteoporotic fracture during each treatment period.

Here the treatment periods represent FIT and FLEX. The patients in the denominators represent

only those patients who enrolled in FLEX, and account for about 15 percent of all patients who completed the FIT three- and four-year studies. The percentage of patients with at least one osteoporotic fracture during FIT ranges from 9.7 to 12.6 percent. Recall that all patients in this time period received alendronate.

When these groups are combined, totaling 10.6 percent, it is still well below the background placebo rate of 21 percent. This background rate differs from the data presented earlier by Dr. Kehoe, as this value represents the background rate for all osteoporotic fractures.

During FLEX, there was an increase in fracture rates compared to FIT, possibly due to differences in the population who chose to enroll in FLEX, and an older patient population that is at higher risk for fracture due to advancing age.

When the alendronate 10 milligram or 5 milligram groups are compared, either individually or combined, it is about the same as those who were re-randomized to placebo. These

1 results will question, from an efficacy
2 perspective, whether there is an advantage of
3 continued therapy beyond four years.
4 To investigate if fracture rates differed
5 when continuing versus stopping alendronate
6 therapy, an FDA exploratory time to fracture
7 analysis was performed using the FLEX data. This
8 analysis included all FLEX subjects, regardless of
9 their baseline fracture status. When looking at
10 all FLEX subjects, no differences across treatment
11 groups were noted. However, a separation is
12 observed in the alendronate 10 milligram group at
13 the tail end of FLEX, and this is equivalent to
14 roughly year 10 of continued therapy for the
15 majority of patients. With an end of 85 in that
16 group, the sample size is too small to draw any
17 conclusions.
18 FLEX patients were then grouped by their
19 T-score at FLEX baseline. Those with a total hip
20 T-score less than or equal to a minus 2.5, who
21 still remained at high risk for fracture after five
22 years of alendronate, are shown here by treatment

group. In the first three years of FLEX, the cumulative incidence of fractures was very similar across all treatment groups. However, by year 3 of FLEX, corresponding to approximately year 8 of continued therapy, we start to see -- I mean, the curves tend to separate across the three treatment groups in favor of those re-randomized to placebo or alendronate 5 milligrams. However, the lines do intersect. Details seen in the previous graph is also seen here. Again, the sample size is quite small, so interpretation is limited, and the impact is unknown.

In a separate post hoc analysis of the FLEX data by Schwartz and others, investigators evaluated if there was any interaction between the femoral neck T-score at FLEX baseline and fracture occurrence. They reported benefit for nonvertebral fractures with a relative risk reduction of 50 percent, but only in a very specific patient population, those without vertebral fractures at baseline who also had a T-score less than a minus 2.5, and no other T-score interactions were noted.

For the Actonel fracture results, we included only those 164 patients that entered the seven-year extension. The top row shows those taking risedronate for the entire seven-year period, and the bottom row shows those patients taking placebo for five years, followed by two years of open label risedronate. Comparing the two groups, the percent of patients with at least one fracture was lower in the risedronate group across all time periods. And the gap seemed to narrow in years 6 to 7, attributable to those patients now taking risedronate. Although the time intervals are unequal, the rates over time in the risedronate seven-year arm appear to decrease, suggesting continued fracture benefit with continuing therapy, but the number of total subjects is relatively small.

The vertebral fracture data for the six years of Reclast are shown here. Patients received either continuous risedronate for six years or for three years followed by placebo. New vertebral fractures were the primary endpoints for the core

study. BMD was the primary endpoint for the extension study, with new vertebral fractures as secondary endpoints.

Continued therapy with Reclast showed a fracture benefit in morphometric vertebral fractures compared to those re-randomized to placebo, with a relative risk reduction of 52 percent, but no difference was seen for the clinical vertebral fractures. These results differ from the Fosamax findings, where a clinical vertebral fracture benefit was seen, but no benefit was seen in the morphometric fracture risk.

These data represent all osteoporotic fractures during the 3-year core study and the extension study for Reclast. No difference in the number of patients with at least one osteoporotic fracture was seen during the first three years of the study since all patients were taking Reclast.

For years 4 to 6, however, a numerical decrease in the number of subjects with fractures was seen in those continuing Reclast therapy. When this difference was tested, the difference was only

borderline significant and did not account for multiplicity. Therefore, no robust fracture benefit could be demonstrated in those continuing therapy.

To look for fracture trends in all patients with prolonged and continuous bisphosphonate exposure, we pooled available fracture data from Fosamax, Actonel, and Reclast, totaling 1200 patients. These 1200 patients represent those who continued active therapy for the entire study duration. However, this number remains small compared to typical fracture studies that enroll anywhere from 7- to 9,000 patients. The analysis did not include patients who were re-randomized to placebo or those who discontinued active therapy.

The number of patients with at least one fracture are grouped into the four exposure time periods based on X-ray time points. Comparing rates over time, there appears to be similar rates, with the exception in years 4 to 5. The reason for improvement in the fracture rate in this time period is unclear, but is likely impacted by the

unequal year distribution. However, the fracture rates for those exposed greater than nine years are similar to those in the original three-year fracture trial, which suggests that there is not a trend toward deterioration in fracture efficacy.

For comparison, the fracture rates for those previously on alendronate and zoledronic acid who switched to placebo are shown. The rates remained constant over time, between 8 to 9 percent. Rates for both groups were still below the background placebo rates.

It should be noted that beyond year 6, the cohort size decreases markedly because of the different study designs and durations of the trials included in the analysis. Overall, these data are not definitive, but raise the question of whether continued fracture benefit is achieved with long-term bisphosphonates when compared with stopping therapy after three to four years.

So to summarize the fracture data, the data seem to show that with continued drug exposure, there is no clear benefit or harm for overall

1 osteoporotic fracture risk. Also, there was no
2 subset with a clear and consistent fracture benefit
3 across the trials, specifically in vertebral
4 fractures.
5 For those re-randomized to placebo who had
6 been previously treated with bisphosphonates who
7 then discontinued therapy, there appears to be no
8 difference in fracture rates compared to those who
9 continued active therapy. In fact, the fracture
10 incidence in this group remain stable in the pooled
11 analysis, suggesting that there is this possible
12 maintenance of benefit after three to five years of
13 previous drug exposure. These results suggest that
14 there is no significant advantage of continuing
15 drug therapy beyond five years.
16 As Dr. Adler pointed out, we do acknowledge
17 that clinicians are being faced with the very real
18 dilemma of managing patients who may want to
19 discontinue therapy. However, there is scant data
20 on a drug holiday. Many scientific opinions have
21 been published about stopping therapy, but these
22 are based on review of studies that did not include

a drug holiday phase. The only available data on a drug holiday is from the Actonel year 8 to 10 extension studies which were recently published. I will now discuss these data in further detail.

Here are the femoral neck BMD results for the 32 patients continuing into years 8 to 10. Up until year 8, patients either received continuous risedronate, on the top in black, or they received placebo for five years, followed by open label risedronate. At the end, the cohort includes 14 patients in this group and 18 patients in the placebo/risedronate group.

BMD results for years 8 to 10 were generally similar to what has been previously presented for continuous therapy, showing maintenance of BMD at the femoral neck and increases in BMD at the lumbar spine.

For those 32 subjects continuing into years 8 to 10, there was only one new fracture at year 8 in the risedronate group, and then in years 9 to 10, there was a similar rate of fractures between the two groups. With such small

numbers, the data are limited and an adequate analysis was not possible.

So regarding a potential drug holiday, there were two published analyses that provide some data on predictive factors at the time of bisphosphonate discontinuation and guidance on subsequent BMD monitoring. A post hoc analysis of the FLEX trial by Schwartz and others, mentioned earlier, also showed that the femoral neck BMD after the first five years of alendronate treatment predicted nonvertebral fractures, but only in a subset of patients, those without baseline vertebral fractures who also had a T-score less than or equal to a minus 2.5.

Also, after looking at fracture risk in those who did or did not lose bone during FIT and seeing no difference, the authors suggested that BMD changes, and therefore BMD monitoring, were not useful in predicting who will benefit from continued alendronate therapy.

The second analysis, an abstract by Bauer and others presented at the 2010 ASBMR annual

meeting, also using the FLEX database, investigated whether serial BMDs at yearly intervals could predict fracture risk. They concluded that total hip BMD at the time alendronate was stopped strongly predicted the risk of clinical fractures over the next five years. In addition, as suggested in the earlier publication, following BMD changes over one- to two-year intervals after alendronate was discontinued were not useful. Dr. Bauer will present more details of his findings later this afternoon.

Based on these reports, BMD at the time bisphosphonates are discontinued may be important in a drug holiday management decision, but there are no studies that define an appropriate drug holiday duration or the utility of surrogate markers of increased risk, particularly since BMD change from year to year is not likely useful.

In the interest of time, I will summarize the next several slides. With bone turnover markers, they show stability on active therapy, while those re-randomized to placebo had gradual

1 increases in markers, but levels generally remained
2 below baseline levels. Bone histomorphometry is
3 available from the Fosamax FLEX study, and overall
4 there was no data to suggest a maleffect of
5 bisphosphonates on bone biopsy parameters following
6 long-term therapy up to 10 years.
7 So, in conclusion, data on the
8 bisphosphonate exposure out to 10 years appear to
9 demonstrate maintenance of BMD at the femoral neck
10 and continued increases in BMD at the lumbar spine.
11 In patients who discontinue bisphosphonates after
12 three to five years of treatment, there are small
13 decreases in BMD followed by a plateau at the
14 femoral neck, and small increases in BMD at the
15 lumbar spine. While the total duration of BMD
16 effect is unknown, change in BMD after
17 bisphosphonate discontinuation is not predictive of
18 future fracture.
19 Fracture data on bisphosphonate exposure out
20 to 10 years appears to demonstrate that there is a
21 plateau in overall fracture benefit after three to
22 four years. There is no clear evidence of harm or

increase in overall osteoporotic fractures, and there is no clear subset with continued benefit, including vertebral. In patients who discontinued bisphosphonate therapy after three to five years, fracture incidence rates were relatively constant over time.

The drug holiday data from control studies are sparse, with limited BMD and fracture results preventing adequate analysis. The available BMD results were similar to what was seen in the long-term studies, although further questions remain to be answered, including who is an appropriate candidate for a drug holiday and what factors should be considered. If therapy is stopped, who should resume therapy, and when?

So in light of the risk/benefit challenges, the available data suggest that therapy can be safely discontinued without loss of efficacy. However, additional data are still needed to further define an appropriate duration of drug cessation and appropriate monitoring. Thank you.

[Applause.]

Clarifying Questions to the Presenters

DR. CARSON: Thank you, Dr. Whitaker. Dr. Whitaker kindly hurried her talk so we could catch up and have enough time for panel questions.

Now, we do have about 10 minutes for the panel to ask some clarifying questions. So I will ask the panel to ask the excellent speakers and presentations clarifying questions rather than discussion questions, just questions that you're confused about or need more information regarding their presentations.

Dr. Cooper?

DR. COOPER: I have a clarifying question for Dr. Whitaker. In your slide set, when you were talking about the analysis of the fracture risk for the subgroup of patients that had a T-score less than minus 2.5 -- I think it was slide 19 in your slide set -- can you clarify? You talked about the T-score less than 2.5 at baseline.

Are you referring to the baseline at their entry into the FLEX study, which was five years after therapy, or their T-score at baseline when

they entered the original trial?

DR. WHITAKER: At the FLEX baseline.

DR. CARSON: Any other questions? Yes, Dr. Orza?

DR. ORZA: I have a question for Dr. Adler. Your figure about 30 to 100 typical fractures prevented for every atypical, was that all typical fractures? And, if so, do you have it for compared to the subset of hip fractures only?

DR. ADLER: No. That was for typical hip fractures.

DR. ORZA: Typical hip only?

DR. ADLER: Yes.

DR. ORZA: Thank you.

DR. CARSON: Yes?

DR. KITTELSON: Thanks. Could I follow up with a question in the same line? I guess, first, to educate me, do we think that bisphosphonates prevent other kinds of fractures, say, of the foot, or wrist, or I guess reduce risk or reduce the severity of those? And is there any evidence, either from surveillance data, from reporting data,

or in the same typical/atypical spirit, that there might be other adverse effects or other beneficial effects that we're not, I guess, hearing about because we're focusing on hip or lumbar spine?

DR. KEHOE: I think I'm going to try to clarify that. In the osteoporosis clinical trials, although morphometric vertebral fracture tends to be the primary endpoint, the nonvertebral fractures and then specifically the hip fractures tend to be secondary endpoints.

When we look at nonvertebral fractures, it generally includes all fractures, including wrist, but ruling out fingers, toes, skull, and that type things, which are general -- the thought is that if you stub your toe and break it, that's not necessarily an osteoporotic fracture. So that's specifically the way the trials are designed. And so all osteoporotic fractures were included in our analyses.

As far as other benefits regarding the drugs, I know there are some issues and some studies out there regarding, in the cancer

populations, whether there is an anti-metastatic benefit. But I think some of those trials have not necessarily shown a clear benefit there.

DR. KITTELSON: So not to move it to discussion or anything, but if we think that there might be something about bisphosphonates that interrupt the bone remodeling process, then it may have some effect on other kinds of fractures also. And so it's not just other benefits -- I guess I didn't want to misstate my question in that way -- but are there also other places where we could be seeing harm from lack of healing or other fractures that just are not behaving the way we might expect?

DR. KEHOE: To my knowledge, we have not seen -- so, obviously, one of the places to look for that is fracture healing in patients that have had fractures. And we have not seen any reports of any consequence about delayed fracture healing. There are some, but they are very small numbers. Whether the osteonecrosis of the jaw is an antiresorptive issue is likely because we have seen

it now with other antiresorptive agents and not just bisphosphonates. So it may be that a lot of these adverse events we're looking at are related to the action of the drug itself.

DR. CARSON: Dr. Johnson?

DR. JOHNSON: Yes. When you were talking about data related to long-term use of bisphosphonates, you said that the FDA AERS data was not terribly useful because it really couldn't give us the data that we needed.

Is there any way of adjusting the data that we receive from this program that would make it more useful to be able to assess long-term use of bisphosphonates? Can adjustments be made by the FDA in this program?

DR. KUYATEH: To clarify your question, are you asking if we can use AERS data to characterize the risk by using --

DR. JOHNSON: Yes, or can you make it such a program that it becomes more useful data?

DR. KUYATEH: Well, it's not that AERS is not useful at all. We do detect signals from this

database. But in terms of characterizing of risk and getting a risk estimate, say, a relative risk or an odds ratio, it's not -- because we cannot infer incidence with these voluntary reports, we can't do that. We have tried in some cases to do reporting rates, but that's as close of a measure to risk as we can get, and there are several limitations to doing that as well.

DR. CARSON: Dr. Winterstein?

DR. WINTERSTEIN: I have a minor clarification question also for Dr. Kuyateh. The long-term utilization data you presented, these were incident users in 2005 who were followed then for five years? Is this correct? Or were these incident users who were assembled over the entire five-year period? That wasn't really clear from your slide, and then I don't understand how you get to 72 months of follow-up.

DR. KUYATEH: Yes. So these were incident users that had a first prescription on or after January 1, 2006.

DR. WINTERSTEIN: And then you followed them

until 2010, which wouldn't give us 72 months of follow-up. I just wanted to make sure that we really have, for every patient, the same amount of follow-up available. It puts into perspective how many long-term users there really are.

DR. KUYATEH: Right. So we don't have the same amount of follow-up for every patient, obviously, because --

DR. WINTERSTEIN: You didn't?

DR. KUYATEH: Right, because --

DR. WINTERSTEIN: Well, if you didn't have the same amount of follow-up, then this graph is useless in terms of determining how many long-term users there are; correct?

DR. KUYATEH: Well, there are limitations to the data, of course. But I'm saying we don't have the same follow-up for each individual because once a patient stops using a bisphosphonate, they pretty much dropped off. Right? So they've been, in a way, censored. But we do get a sense for how long --

DR. STAFFA: Let me jump in. I think I can

1 help with that, Dr. Winterstein.
2 Basically, what we tried to do here is to go
3 beyond the typical insurance claims databases and
4 to use something that was pharmacy-based. So that
5 way we get all payors and we get outside the
6 limitations of specific formularies. But as you
7 know, there's no enrollment data at the pharmacy
8 level, so we're challenged to know whether patients
9 are actually still there to fill prescriptions if
10 they receive them.
11 So what we did was several steps to try to
12 make sure that patients were actually in the system
13 receiving prescriptions from that pharmacy at the
14 beginning of the period and at the end of the
15 period, and then tried to look at their
16 bisphosphonate prescriptions throughout that
17 period. By doing that, we're actually limiting it
18 to patients who probably take other drugs as well
19 since they'd have to be there to be getting other
20 prescriptions filled rather than just
21 bisphosphonates.
22 So this is really a crude look, but when we

1 looked at the literature, we found that the results
2 were very, very similar to systems that actually
3 had enrollment data. So we think that maybe
4 they're at least in the right ballpark. But you're
5 right. There are limitations to what we can
6 conclude from that.
7 DR. WINTERSTEIN: Okay. But, essentially,
8 every patient had a pharmacy record -- some type of
9 pharmacy record data from 2005 to 2010, so they
10 weren't censored. So you were fairly sure that
11 they were filling prescriptions over a five-year
12 time period. I still don't know how you get 72
13 months out of this, but you had some type of
14 five-year follow-up, essentially.
15 DR. KUYATEH: That's correct. So the
16 patient, in order to be eligible as an incident
17 user, to be eligible for the analysis, they had to
18 have a prescription in three different time
19 periods, so at the beginning of the study period,
20 at the middle, and at the end. And it had to
21 be -- it could be for any drug, not just the
22 bisphosphonates that we were focused on, to make

sure that they were in the system and they were being followed. So that's correct.

DR. CARSON: We have time for one last question, but no answer. No, just teasing.

[Laughter.]

DR. CARSON: Dr. Suarez-Almazor?

DR. SUAREZ-ALMAZOR: Yes. I was wondering if the FDA had attempted to pull some of this data, or even to assign some health utility values to it. At the end of the day, what we need to know, I think, is how many deleterious events occur if a patient is treated and how many occur if a patient is not treated. And Dr. Adler discussed that briefly with respect to fractures.

I think that some of the other data, esophageal cancer and so forth, could also be added to some sort of modeling. But I think that at the end, that's what is important to us, is to know if we don't treat a patient, what are the chances that a bad event occurs? And if we treat them, what's that probability as well?

So I don't know if any attempt has been done

to combine risks and benefits in such a way.

DR. STAFFA: I can take a shot at that one. I think one of the challenges is that, as you've seen, you can try to pull some of the trial data together, which can look at the benefit information in large groups of patients. But some of these safety issues are so rare, we don't see them in the trials necessarily when you get down to the small numbers that Dr. Whitaker presented. So then we flip over to epidemiologic data to try to see those, and it's very difficult to combine those two different types of data.

DR. CARSON: Thank you. And thank you very much to the speakers this morning for excellent and clear presentations.

We'll take a break now. And may I remind panel members not to speak about any of the issues regarding this meeting among yourselves or to any members of the audience. And please return at 10:15 for our next presentation.

(Whereupon, a brief recess was taken.)

DR. CARSON: We will now proceed with the

presentation from our guest speaker. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Our next speaker is Dr. Douglas Bauer, who's a professor in the Department of Medicine at the University of California San Francisco. He will discuss fracture risk after discontinuation of bisphosphonates.

Dr. Bauer?

Guest Speaker Presentation - Douglas Bauer

DR. BAUER: Well, good morning. First of all, I want to say thank you for being invited to this very important meeting. Let's see if I can figure out how to advance the slides. There we go.

My disclosures are here, and it's important to note that much of the data I'm going to present here will come from the FIT and FLEX trial, which, as you heard, was funded by Merck, but actually was independently coordinated by our group at UCSF, and that the corporate sponsor really had no role in

the analysis or interpretation of the data that I'm going to show.

So like Dr. Adler, I am a clinician. I'm actually a primary care physician, a general medicine practitioner at UCSF. This is an issue that is really front and center in primary care. Many of our patients are calling, asking what to do about long-term use of bisphosphonates. Should they stop? Should they take a drug holiday? What's to be done? And there's been some published reports by experts in our field that suggest that a drug holiday and monitoring with either bone mineral density or bone turnover markers, or BTMs, should be done after five years of bisphosphonate.

As a clinician, though, I'd ask the following questions, which I think we have in part addressed, and I'm going to try to tackle the last two. The first one is, compared to continued bisphosphonate therapy, what's the risk of fracture after discontinuation? And I think Dr. Whitaker's analysis has shed some light on this issue.

The second question is, what factors predict

fracture among those that have discontinued? And finally, is monitoring after discontinued, either with bone mineral density or other surrogate markers such as bone turnover markers, clinically useful?

I would argue that the ideal way to study this is to look within an existing randomized controlled trial where subjects were randomized to bisphosphonate versus placebo, and then the bisphosphonate group was re-randomized to either continue therapy for a prolonged period of time or stopped, switched to placebo in a blinded fashion. The study was sufficiently large to look at fracture outcomes. Unfortunately, there are no ideal studies to address this issue, but there are two studies, one of which is published, which come close.

This is the overall design of the FIT and FLEX trial, which I will just quickly remind you that the FIT study was a study of postmenopausal women that were randomized to either alendronate or placebo and followed for an average of 3 and a half

1 to 4.5 years. Individuals who were eligible to be
2 randomized to FLEX were in the alendronate group.
3 The individuals were offered open label alendronate
4 after the completion of FIT, and then re-randomized
5 to either continue alendronate or be switched to
6 placebo. And it's important to note that this was
7 all done in a triple blind fashion. Neither the
8 investigators nor the participants knew what they
9 were receiving in FLEX.
10 A couple of other points that weren't
11 addressed by the very nice FDA presentation was the
12 switch in FIT from 5 milligrams to 10 milligrams
13 occurred in a blinded fashion. So, again, neither
14 the participants nor the investigators were aware
15 of which individuals were in placebo and which
16 received alendronate. They all received at least
17 three years of alendronate to be eligible to be
18 randomized into FLEX.
19 Importantly, individuals in FLEX were only
20 eligible if their T-score was at least a minus 3.5
21 at FLEX baseline. And, in addition, their bone
22 mineral density had to be greater than their FIT

baseline, meaning they could not have lost overall bone, as measured by bone mineral density, during the FIT study and still be eligible for the FLEX study. So I think these were important caveats to remember.

As previously mentioned, women were re-randomized then to either placebo or alendronate. They did all continue to receive calcium and vitamin D. As was previously mentioned, the primary endpoint was total hip bone mineral density. But the other endpoints are listed here, and those included fractures, which were actually listed as a safety endpoint. But, in fact, these were reviewed and adjudicated with the same rigor as fractures during the fracture intervention trial, again in a blinded fashion.

In addition, we also measured bone turnover markers. These were done using stored serum and urine. This is an important point. They measured urine NTx, which is a bone resorption marker, as well as bone-specific alkaline phosphatase, which is a biomarker for bone formation. And the

important point about these biomarkers is that these are thought to be integrally related to the mode of action of bisphosphonates; that is, they measure levels of bone turnover.

This is data that you've already seen, but it's shown in a slightly different fashion. So these are women that are randomized either to placebo in white or continued alendronate in the FLEX study, but now showing their bone mineral density, in this case the femoral neck, both in the FIT study, shown here on the left, as well as the FLEX study on the right.

As has been shown in other bisphosphonate trials, you see the increase in bone mineral density during bisphosphonate therapy. And this study was about a 4 percent increase in femoral neck bone mineral density, and then after re-randomization to either continued alendronate, shown here, or re-randomization to placebo, shown here. There's the previously mentioned gradual loss of femoral neck bone mineral density, which was statistically significant and was about a

2 percent difference after five years. So this is data that you've seen.

You see a similar but slightly different outcome. Now, this is looking at total hip, again, another hip bone mineral density site, which showed, again, continuation and preservation of bone mineral density after re-randomization to alendronate in the FLEX study shown here, but a continued loss of total hip bone mineral density, which was statistically different at the end of five years with about 3 percent difference between the treatment groups.

Note that the total hip bone mineral density actually was similar to the bone mineral density at the beginning of randomization to FIT; so slightly different than the femoral neck data. But the clinical significance of this and whether this really is important is unclear.

Now, this is the bone turnover data that I mentioned. And I'd like to point out that this is similar to data that would be seen in many of the randomized trials of bisphosphonates during the

first five years. Again, these are women who are randomized in FLEX, but this is their bone turnover data during FIT; so, again, during the first five years when all the women received alendronate.

You can see that there's a prompt reduction in this biomarker of bone resorption. This is urinary NTx. As you can see, there's about a 60 to 70 percent reduction in the first year, and this is maintained during the continuation of FIT for five years. And then after re-randomization to either continued alendronate or to a placebo, you can see that there is a gradual but small increase in the urinary NTx levels as compared to continued suppression in the placebo group. Now, it's important to note that this is on an absolute scale, so note that these are units of NTx.

In the next slide, I've actually shown you on a percent scale. So this is the same data as in the previous slide during FLEX, but now represented as the percent change in NTx from the beginning of FLEX, shown here, to the end of FLEX.

As you can see, there's about a 25 percent

increase in the urinary NTx over the course of five years of receiving placebo after having received five years of alendronate. It's also interesting to note that actually most of the increase occurred in the first year, and then appeared to be relatively stable during the subsequent four years.

This is the fracture endpoint data, which, again, was an exploratory endpoint in FLEX but was looked at with great rigor. And this is shown in a slightly different format than the FDA presentation, but as you can see, the results and conclusions are similar. The relative risk of non-spine fracture was 1.0, so it was similar whether you received continued alendronate or switched to placebo. We also looked at hip fracture, but, of course, this is really too small and underpowered to make any definitive impressions. But the rates were similar.

As was previously mentioned, we looked specifically at two types of vertebral fracture during the FLEX study, first, morphometric vertebral fracture, which occurred in about

10 percent of the women during the FLEX follow-up. As you can see, there was no increased risk in the women that were switched to placebo. But there was about a 50 percent increased risk of clinical vertebral fractures, and these are vertebral fractures that first came to the attention of a participant's physician and then were confirmed centrally in the study. Notice that those happen with considerably less frequency than either the morphometric fractures or the non-spine fractures.

So as a clinician, I am going to talk a little bit more now about this group that were randomized to placebo and ask the questions about, can you predict fractures in that group, and can you use some sort of monitoring to identify those who will fracture?

So this is data that was presented at ASBMR. It has not yet been published. But this is now an analysis of the placebo women in FLEX, stratified by whether they had a fracture during FLEX, and that's the 94 women here, or did not have a fracture during FLEX, shown here.

Now, the 94 women that had a fracture in FLEX, this included women that had both a clinical spine fracture or a nonvertebral fracture. And as you can see, women had roughly the similar exposure to previous alendronate, approximately five years, which is as previously mentioned.

As you would expect from the epidemiology of vertebral fractures, women who fractured tended to be older. It was statistically significantly different. They also were more likely to have a baseline vertebral fracture at FLEX baseline, and their bone mineral density was significantly lower. Again, this is women that had fractures during FLEX.

It's interesting to note that the likelihood of having BMD osteoporosis, that is, a T-score less than minus 2.5, was about twofold higher in those that had a subsequent fracture in FLEX compared to the women that did not have a fracture. And as you can see, the baseline levels of bone alkaline phosphatase here and urine NTx were similar in the two groups.

Let's see. My monitor just went blank. But that's okay; I can do without it.

So the next set of analyses are going to ask this question: Do bone mineral density or BTM measurements at the time of discontinuation of alendronate predict fracture outcomes in the subsequent -- in next five years?

This is a complicated slide, but I'll walk you through it. This is now the relationship between baseline bone mineral density at the beginning of FIT [sic], and the likelihood of having any clinical fracture during the five years of follow-up in FLEX. Sorry, I said FIT, but I meant FLEX. This is now baseline bone mineral density at the beginning of FLEX, and then the likelihood of any clinical fracture during five years of follow-up during FLEX.

This is baseline bone mineral density here. The femoral neck is -- excuse me. The total hip is divided into tertiles. So women in red had the lowest bone mineral density; and, unfortunately, the T-scores -- which don't show up well here

because they're embedded in the slide -- are shown here. But I believe they show up better in your handout, are shown at the bottom.

So these women in red here had the lowest bone mineral density at the beginning of FLEX. Women in green over here had the highest. And as you can see, there's a strong relationship between baseline bone mineral density at FLEX baseline and your subsequent likelihood of having a fracture during FLEX. These analyses, by the way, are all adjusted for age and for the presence or absence of a vertebral fracture at the beginning of FLEX.

This data was similar, by the way, for femoral neck. Interestingly, bone turnover, as assessed here by NTx levels, did not predict who was going to have a fracture during FLEX in the placebo group. So, again, this is the five-year fracture experience on this axis by tertile of bone turnover. In this case it's NTx, and as you can see, individuals here with the lowest NTx had a similar fracture experience during five years as those that had the higher levels of NTx at

baseline. These results were similar looking at another bone marker, bone-specific alkaline phosphatase. But I won't show you those data.

Now, the second question is, do 1- to 2-year changes in bone mineral density or bone turnover after discontinuation predict incidence of fractures? The analysis is similar, with the same groups and the same type of analysis. But now we're looking at a one-year change in bone mineral density after baseline FLEX, and the relationship to any clinical fracture during the total of five years of follow-up.

Here we again saw no relationship between short-term changes in bone mineral density and the likelihood of developing a fracture during FLEX after discontinuation of alendronate. Remember that these are the placebo group patients.

These individuals over here on the left -- I can't read my own writing from this distance, but I believe that these are the women that have the greatest reductions in bone density in the first year, and the women over in green here had the

1 least reductions in bone density during the one
2 year. And as you can see, the rates are quite
3 similar. Again, the results were similar using
4 femoral neck bone mineral density.
5 These are the relationship between short-
6 term changes, one-year changes in bone turnover, in
7 this case, NTx, relating those short-term changes
8 to the likelihood of a fracture during five years
9 in FLEX. And, again, as you can see, there's no
10 relationship between short-term changes, one-year
11 changes in NTx, and the likelihood of having a
12 clinical fracture during FLEX follow-up after
13 discontinuation of alendronate.
14 These results were similar for bone alkaline
15 phosphatase, the other bone marker that we looked
16 at. And in addition, we also looked at two-year
17 change in bone mineral density and two-year change
18 in bone turnover markers, specifically NTx and
19 bone-specific alkaline phosphatase, and the results
20 were qualitatively similar.
21 Now, as I mentioned, there's no ideal study.
22 FLEX does have a couple of important strengths, I

1 think. It is the only currently published study
2 that looked at individuals who were randomized to
3 either continuation or a discontinuation, it was
4 prolonged and blinded after discontinuation, and
5 that the fractures were objectively documented in a
6 blinded fashion during follow-up. But there are
7 some limitations that I want to point out to FLEX.
8 First of all, as has been previously
9 mentioned, fracture outcomes during FLEX were not a
10 primary outcome. And, in fact, we had relatively
11 low power to look at fracture outcomes. And that's
12 particularly true for subgroups that might have had
13 really exaggerated responses, so those women that
14 lost a lot of bone during FLEX or had really
15 exaggerated responses in bone turnover, we were
16 underpowered to detect any effect on fractures.
17 Some of the newer bone turnover markers such
18 as P1NP and CTX were not available, at least not in
19 every single visit in FLEX. We have actually
20 reported some of the post hoc analyses, looking at
21 P1NP and CTX, but those measurements were not
22 available at the time points that I've shown you in

this data.

Finally, the results only apply to older women who were treated with daily alendronate for approximately five years. And based on pharmacokinetic data, I think it's highly likely that these results are also generalizable to weekly alendronate. But the question, which you'll hear about, I believe, from other speakers as well, is are these generalizable to other bisphosphonates?

As you've heard from Dr. Whitaker and others, the HORIZON extension, which is the zoledronic acid study, which was very similar to the FLEX design, randomized women after three years of zoledronic acid to either continue for another three years or be switched to placebo. And as has been previously mentioned, the fracture rates were very similar to those observed in FLEX; that is, nonvertebral rates were similar, and morphometric vertebral fractures showed about a 50 percent increase in those -- or there was about a 50 percent reduction that was continued on zoledronic acid compared to those that were

1 switched to a placebo. Interestingly, as was noted
2 in the previous presentation, that relationship was
3 not seen for clinical vertebral fractures as was
4 seen in FLEX.
5 As far as I'm aware, there's no randomized
6 continuation versus discontinuation for other
7 bisphosphonates. And I personally have some
8 concerns about generalizing to other
9 bisphosphonates, given the known pharmacokinetic
10 differences between the bisphosphonates. So while
11 I applaud the FDA's efforts to pool these data, I
12 really think that the question about whether it's
13 appropriate to be pooling discontinuation data,
14 given the known differences in pharmacokinetics, I
15 think is an important issue for discussion.
16 So just to summarize here, discontinuation,
17 specifically of alendronate, since that is the data
18 that I'm most familiar with, which is from FIT and
19 FLEX, compared to alendronate therapy for 10 years,
20 discontinuation in five years is associated, in
21 fact, with modest reductions in hip bone mineral
22 density, particularly if you look at the total hip

bone mineral density.

There are modest increases in bone turnover that are detectable and statistically significant. There is an increased risk of clinical vertebral fractures; however, this was not seen for morphometric vertebral fractures. There was no increase in the risk of non-spine fractures. And I would argue that these data are qualitatively similar, at least for non-spine fractures, in the zoledronic acid study.

Finally, in addition to age and existing vertebral fracture, after discontinuation of prolonged alendronate therapy, hip bone mineral density is a strong predictor of fracture risk. Interestingly, it is not related to levels of bone turnover at the time of discontinuation. And perhaps even more disappointing for those that are interested in monitoring, there was no evidence that short-term changes in either bone mineral density or bone turnover, at least as measured by NTx and bone-specific alkaline phosphatase, were able to predict the individuals who were going to

have a fracture once they discontinued five years of alendronate. And, again, this suggests that monitoring is not particularly useful, and, in fact, may be counterproductive.

To summarize a little bit from a clinical standpoint, though, I would argue that continuation of alendronate therapy for at least five years, given the data from FIT and FLEX, may be prudent among individuals that are at particularly high risk of fracture. And I would argue that those individuals are those that have had a previous hip or vertebral fracture.

Based primarily on the subgroup analysis which was published in the Schwartz paper, individuals that continue to have low bone mineral density, specifically T-scores that are less than minus 2.5 after completing five years of alendronate therapy, would be candidates for continued therapy.

I think I'll stop there, and I appreciate your attention. Thank you.

[Applause.]

Clarifying Questions to the Presenters

DR. CARSON: Thank you, Dr. Bauer. I'll ask you to remain there to address any questions the panel has.

Panel? Dr. Johnson?

DR. JOHNSON: Yes. Thank you for your presentation.

In regards to your demonstration that there may be individuals at greater risk for fracture, showing that those with the baseline total bone mineral density that was the worst showed a higher risk of fracture, do you know what the N was there? I'm wondering if we can break that down any further in looking at what minus --

DR. BAUER: I'm sorry. Can you refer to a specific slide? I'm not sure I know exactly what you're talking about.

DR. JOHNSON: I'm sorry?

DR. BAUER: Could you refer to -- are you referring to a specific slide?

DR. JOHNSON: I am. It would be your first graph slide. Keep going. That one.

So could you break it down any further in terms of who's at risk, greatest risk, going up to minus 2.5 or even higher? Because this may be important in knowing who should continue on medication versus who can stop medication.

DR. BAUER: Okay.

DR. JOHNSON: And then, secondly, you said baseline, but is this baseline at beginning of FLEX or beginning of FIT?

DR. BAUER: Yes, I'm sorry. I probably went through this too quickly because it's really important.

This is after five years of alendronate therapy. The placebo group that was -- yes, five years of alendronate therapy that then were randomized to placebo. So these women had all completed five years of alendronate, and then over the subsequent five years, they received placebo.

This is their bone mineral density at the time of discontinuation. All right? So this is the beginning of FLEX. All right? And what this clearly shows is that your bone mineral density at

the time that you discontinue alendronate is strongly predictive of whether you're going to have a fracture or not during the subsequent five years.

I'm sorry. I didn't quite understand your question about whether --

DR. JOHNSON: Yes. Can you break it down any further? You have the women at risk appear to be those with lowest bone density, so the minus 3.5 to minus 2.1. Did you break it down any further to see if there's any point at which it really rises?

DR. BAUER: No. And remember that the total number of fractures here that we are looking at is 94. So I think looking for thresholds is a dicey business. So, in fact, we, a priori, decided to look by tertiles, which is this data that I've shown you here. And remember that this T-score on the bottom end is limited by the entry criteria to FLEX. If your T-score was worse than minus 3.5, you weren't eligible. And then these are just looking by T-scores.

If you look at this by deciles, it's actually some noise, but it does appear to be a

clear monotonic relationship, and I don't think there's really evidence of a threshold.

DR. CARSON: Dr. Suarez-Almazor?

DR. SUAREZ-ALMAZOR: Yes. If we stay on this slide for a second, and I realize the numbers are small, but what I would like to see is exactly the same bars for those who actually received the drug, not just the placebo group. So according to their baseline BMD, what the fracture rate was. Because this is just for the placebo group, but what happened with those who continued the drug? Because that's what would indicate whether it was useful or not continuing it.

DR. BAUER: Yes, that's true. And, in fact, those results, I believe, were at least mentioned in the FDA presentation. It's a slightly different question, actually. That question is trying to -- reflects on the question, should I stop or not? This is looking at women who have stopped, and the question is, can I predict who is going to have a fracture? And, therefore, should I use some sort of risk algorithm or monitoring to detect to

1 try to pick up individuals that in fact I might
2 wish to revisit that decision?
3 So the analysis that you're talking about in
4 fact has been published both in the original paper
5 by Black et al. in JAMA, as well as further
6 analyses were looked at by Schwartz et al. in JBMR.
7 And what those showed was that for non-spine
8 fractures, there was no evidence of continued
9 benefit after five years, so there was no
10 difference.
11 That's the risk ratios that I showed earlier
12 here. The relative risk is 1.0. But there were
13 subsequent subgroup analyses that showed that among
14 women who did not have a vertebral fracture at
15 baseline and continued to have a very low bone
16 mineral density after five years of
17 alendronate -- that is, a T-score of minus 2.5 or
18 worse -- in fact, the risk ratio -- there was a
19 statistically significant interaction suggesting
20 that continued alendronate therapy was useful in
21 that subgroup but not in the overall subgroup.
22 And, again, that was mentioned in the FDA

presentation as well, and I believe that data was in the handout, or certainly is in the materials.

DR. SUAREZ-ALMAZOR: Yes. No, I understand that for the question that you posed --

DR. BAUER: Right.

DR. SUAREZ-ALMAZOR: -- only that data would be useful to answer it. But for what we are evaluating at large, I think that having the side-by-side graph that shows what happens for those who receive the drug at different levels of BMD would be useful in judging whether continuing the drug or taking a drug holiday is appropriate. So I don't know if that analysis has been done and can be shown to us.

DR. CARSON: Dr. Whitaker, do you have any information regarding that?

DR. KEHOE: It's going to be in our backup slides.

DR. BAUER: Yes. The gentlemen here is saying that they're going to show this from Merck presentation. But I believe that data actually was the paper by Black et al. in JAMA. There's a table

looking at subgroup analysis by BMD at the time of discontinuation, and I believe that data is available. First author is Black, and it was in JAMA.

DR. CARSON: While Dr. Whitaker is looking, let's go on to the next question.

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: I had exactly the same question. And just to clarify, while they are looking, that means that the conclusions would be consistent from the two presentations. So I think that's important, the same conclusion about the role, using BMD as a predictor.

DR. CARSON: Okay. Do you have that?

DR. KEHOE: I think we're going to look for our backup slide 42.

DR. CARSON: Drug backup slide 42.

DR. KEHOE: Can you pull up 43?

So this is the patients -- I think you're asking based on what their BMD was at FLEX baseline, what happens over time.

DR. SUAREZ-ALMAZOR: Yes, because it could

be that those patients who had almost normal BMD, there would be no point in continuing. But for those who had a T-score below 3.5, minus 3.5, in those patients perhaps we could avoid fractures by continuing the use of the drug.

DR. KEHOE: So in our original presentation we showed those with a T-score of minus 2.5. This is looking at patients who have a T-score between minus 1 and minus 2.5, and the time to event based on the three drug groups.

DR. SUAREZ-ALMAZOR: Okay.

DR. CARSON: So help us get -- this is at the beginning of FLEX, and it's with just the placebo and two different doses, right?

DR. KEHOE: Correct.

DR. CARSON: So it shows no difference? Is that --

DR. KEHOE: It appears that way.

DR. SUAREZ-ALMAZOR: Okay. But we don't know for BMDs below that value what happened. We don't have the data available right now.

DR. KEHOE: That was our presentation

slide --

DR. CARSON: And you mean BMD is more negative, right?

DR. KEHOE: Yes. That would be slide 19 from the FDA efficacy presentation.

DR. CARSON: What number was that?

DR. KEHOE: Slide 19. So this is looking at patients who at the back and forth of FLEX were in the osteoporotic range, a BMD T-score of less than minus 2.5. And you can see black is alendronate, green is placebo, and alendronate 10 is black, alendronate 5 is red.

DR. SUAREZ-ALMAZOR: So there is a trend for those who were on alendronate to actually have more fractures -- I mean, very similar, but --

DR. KEHOE: Well, the numbers are getting so small, we don't feel comfortable saying that there's a worsening here.

DR. SUAREZ-ALMAZOR: Yes. Okay.

DR. KEHOE: We just feel that they're consistent among all groups.

DR. BAUER: Theresa, could you clarify what

the outcome is here? Is it any osteoporotic fracture?

DR. KEHOE: This is any osteoporotic fracture. So this is morphometric as well as any clinical fracture.

DR. BAUER: I think that's in important distinction to point out. Remember, the published FLEX data actually has looked specifically at, really, three fracture outcomes: any non-spine, morphometric vertebral fractures, and clinical vertebral fractures. So those are different. I hadn't actually seen this analysis till just this morning, and I am somewhat surprised by this. But we'll have to go back and look and see if we've done a similar analysis. But the published data that we've looked at looked specifically at non-spine fractures, and then separated vertebral fractures into morphometric and clinical fractures.

The interaction that I'm speaking of was only in the individuals that did not have a vertebral fracture at baseline and had low hip bone mineral density at the beginning of FLEX. Among

1 those individuals, their likelihood of having a
2 non-spine fracture was higher if they discontinued
3 alendronate compared to if they continued.
4 There was no evidence of interaction with
5 any of the vertebral fracture outcomes. So either
6 morphometric or clinical spine, in fact, bone
7 mineral density did not -- there was no interaction
8 with that outcome. And, again, I don't believe, at
9 least not as I'm aware, we did not actually do a
10 composite outcome such as this.
11 DR. CARSON: Dr. Cooper?
12 DR. COOPER: Dr. Bauer, in slide 20 of your
13 presentation, you talk a little bit about how
14 you're hesitant to pool the data based on the
15 pharmacokinetic differences between the
16 bisphosphonates. Could you expand on that just a
17 little bit to help us understand about why you're
18 hesitant to do that based on those
19 pharmacokinetics?
20 DR. BAUER: Sure. Well, first of all,
21 there's never been a head-to-head fracture outcome
22 study for efficacy, and there's much, much less

1 data about resolution of effect. And many people
2 in the audience can actually speak to this better
3 than I. There are differences between the
4 bisphosphonates in terms of their pharmacokinetics
5 that would suggest that their resolution of effect
6 in fact might differ quite substantially.
7 So although I think it's useful, I'm not
8 sure -- for an individual clinician, it would be
9 wise not to take into account specifically which
10 bisphosphonate they've been exposed to for the
11 duration of time before discontinuation and
12 assessing it.
13 I think perhaps some of the other industry
14 representatives here may specifically talk about
15 the different pharmacokinetic differences. But
16 certainly there has been a lot of argument about
17 which bisphosphonate works quicker, which
18 bisphosphonate has more resolution of effect
19 quickly. Dr. Adler actually mentioned this in
20 terms of the year-end levels being different after
21 14 months in risedronate- and alendronate-treated
22 women. And I think this is something that, really,

there's just very, very little published data.

DR. CARSON: Final question, Dr. Madigan.

DR. MADIGAN: I'm just curious. You showed, in the placebo group in FLEX, there's clear predictors of fracture. Do you have any sense or has that been -- any sense of the predictive performance, sensitivity, specificity, area under the curve?

DR. BAUER: Not in that way. We actually did do number needed to treat analyses, and those are published in the Schwartz paper, et al. And the women that had low bone mineral density less than 2.5, again, women did not have a vertebral fracture in FLEX at baseline, but had a BMD T-score that was 2.5 or worse at the beginning of the FLEX. The number needed to treat to prevent a recurrent fracture was 8. We haven't actually done the sensitivity, specificity, or ROC analyses, though.

DR. CARSON: Thank you, Dr. Bauer.

It's now time for the presentations by the sponsors. This is an unusual meeting in that we not only have two advisory committees meeting, but

we have four sponsors presenting today.

I do remind public observers that at this meeting, it is an open meeting for the public observation. Public attendees may not participate except at the specific request of the panel.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meetings, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsors' non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of this meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the

committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

So with that said, let's move on to our first sponsor presentation, which will be by Dr. Arthur Santora, who's the executive director of clinical research, diabetes, and endocrinology at Merck Research Laboratory.

Sponsor Presentation - Arthur Santora

DR. SANTORA: Good morning. I'm Art Santora from Merck clinical research, and I'd like to thank the FDA for giving Merck the opportunity to comment on two very important topics. I'd also like to give the previous speakers thanks because they left a few things for me to say about the alendronate long-term trials, and also their excellent descriptions of the studies.

First, what data support long-term treatment with alendronate? When alendronate is used in accordance with the prescribing information for the

1 treatment of osteoporosis in postmenopausal women,
2 10-year clinical fracture data support a favorable
3 benefit to risk profile in osteoporotic patients
4 who remain at risk of fracture.
5 Second, on the question of drug holiday, the
6 determination that a patient requires long-term
7 treatment should be made by the treating physician
8 based on the patient's individual characteristics.
9 A drug holiday may be considered for patients who
10 are no longer considered to have sufficiently high
11 fracture risk. However, neither restricting the
12 duration of use nor implementing a drug holiday is
13 likely to be beneficial for patients who remain at
14 sufficiently high fracture risk and who require
15 long-term treatment.
16 Evidence supporting the long-term use of
17 alendronate are shown on this slide. Two 10-year
18 trials of alendronate have compared the effects of
19 discontinuing versus continuing treatment for five
20 years. The phase 3 studies on long-term extensions
21 enrolled 350 women from the base study, FIT, and
22 the long-term extension study, FLEX, enrolled

1,099. Between these two studies, 897 patients received alendronate, of whom 587 completed 10 years of study.

In FLEX, patients who had previously been treated with alendronate for five years, continued treatment for five more years, reduced the risk of clinical vertebral fracture by 55 percent. And in a subgroup analysis I'm going to show reduced nonvertebral fracture risk by 39 percent in those patients who entered FLEX with a femoral neck BMD T-score less than minus 2. Continued treatment maintained hip BMD and increased spine BMD and maintained bone turnover at a stable level that did not wane or progress over 10 years of treatment.

In contrast, discontinuation of alendronate after five years led to loss of hip BMD and stable spine BMD. Discontinuation resulted in an increase in bone turnover to a level only slightly lower than pretreatment. The safety profile during the five-year extensions, that is, through 10 years of continuous treatment, was consistent with that established in studies up to four years long.

Regarding adverse events of specific interest to this meeting, in clinical studies up to 10 years, there were no reports of osteonecrosis of the jaw; subtrochanteric and diaphyseal femur fractures were infrequent, with no difference in risk between drug and placebo groups; and there were two reports of esophageal cancer, both after short-term use.

I'll briefly review the phase 3 studies in FIT as background to the presentation of the long-term extensions.

A pooled analysis of the three-year phase 3 studies is shown on this slide. In the left panels, an increase in lumbar spine BMD of approximately 8 percent was observed with the 10 milligram daily group, shown in yellow lines and boxes, versus a small decrease with placebo. Femoral neck BMD increased by about 4 percent, again versus a 1 percent decrease with placebo. Most important, the risk of new vertebral fractures was reduced by 48 percent in patients treated with alendronate.

1 The fracture intervention trial provides a
2 richer source of information on the effects of
3 alendronate on fracture risk. FIT was actually two
4 studies with a common recruitment and endpoint
5 assessment procedure. All patients were
6 postmenopausal women with low hip BMD. And I think
7 it's important to note that the BMD entry criteria
8 was minus 1.6. So FIT includes a cohort of both
9 osteoporotic and osteopenic women, and the results
10 should be interpreted in that light.
11 Patients with prior vertebral fracture were
12 enrolled in the 2,027 patient vertebral fracture
13 study and treated with alendronate or placebo over
14 three years; 4,432 women without a prior vertebral
15 fracture were enrolled in the clinical fracture
16 study and treated for an average of 4 and a quarter
17 years. Both morphometric spine fractures and all
18 clinical fractures were evaluated in both studies.
19 This slide illustrates the risk reduction in
20 fracture at multiple sites observed during the
21 three-year vertebral fracture study. Starting from
22 the left pair of bars, treatment with alendronate

reduced the risk of morphometric vertebral fractures, that is, those detected by X-ray, by 47 percent, and reduced the risk of clinical fractures, identified by acute onset of pain with X-ray confirmation, by 54 percent. Multiple or morphometric fractures were reduced by 90 percent and clinical fractures at any skeletal site reduced by 26 percent. Most important, the risk of hip fractures was reduced by 51 percent.

Fracture risk in the four-year clinical fracture study is shown for the osteoporotic cohort, that is, those with a hip/neck BMD T-score less than minus 2.0. Morphometric vertebral fractures were reduced by 48 percent, and multiple morphometric fractures reduced by 78 percent. Risk of any clinical fractures were reduced by 22 percent; however, clinical, vertebral, and hip fracture risk was not significantly lower with alendronate.

The pharmacokinetics of alendronate, including long-term bone uptake and release, are often misunderstood. I'd like to review a few key

points that have important implications for long-term treatment.

Following absorption, about 50 percent of the absorbed dose is rapidly excreted in the urine and 50 percent found in bone. The autoradiograph shows the distribution of tritium-labeled alendronate 4 hours post-dose in this rat study. The black dots representing alendronate, indicated by the orange arrows, are concentrated under bone-resorbing osteoclasts, identified by the yellow arrows, at about ninefold higher level than found under bone-forming osteoclasts.

Only alendronate on the surface of bone inhibits osteoclasts. That's a key point to remember when considering how effects persist. Alendronate on the surface of bone is either slowly released into blood or trapped within newly-formed bone, where it does not inhibit osteoclasts on the bone surface. The estimated half-life on the surface of bone is between two and five weeks. I would comment that only alendronate has had a terminal elimination study done to determine what

1 the terminal elimination is.

2 This is the half-life on the surface of

3 bone. So some alendronate is retained in bone, and

4 osteoclasts may release that alendronate trapped in

5 bone. The amount of alendronate released depends

6 on prior dose and duration of treatment. Modeling

7 of clinical pharmacology data predicts that the

8 amount released from bone will blunt the loss of

9 bone, but be insufficient to fully prevent bone

10 loss if alendronate is discontinued after only 5 to

11 10 years.

12 For example, after five years of treatment

13 with 10 milligrams daily, the amount released from

14 bone each day is approximately the same as that

15 absorbed after a 1.7-milligram daily dose. After

16 10 years, the amount released is approximately the

17 same as that absorbed after a 2.5-milligram daily

18 dose, which is only 25 percent of the approved

19 10-milligram osteoporosis treatment dose. Data

20 from clinical studies of treatment discontinuation

21 are consistent with these estimates.

22 In a recently completed study of patients

previously treated with bisphosphonates for slightly more than five years on average, discontinuation of treatment resulted in a prompt increase in the bone resorption marker NTx within one month, as illustrated by the white dashed lines. Continued treatment with alendronate, in this case 70 milligrams weekly, maintained bone resorption at the same level as previously shown at the start of the study. The 60 percent increase by month 12 is still about 20 percent lower than that estimated as the pretreatment bone resorption level, indicating a small residual effect due to prior therapy.

The long-term extensions of the phase 3 studies provide the answer to the question, what happens to BMD when treatment with alendronate is discontinued or continued for five more years? The left panel illustrates the increase in lumbar spine BMD by approximately 14 percent during continued treatment with alendronate, 10 milligrams daily for 10 years. Hip/neck BMD is maintained if treatment is continued, but decreases if alendronate is

stopped.

The FIT long-term extension study provides additional information on fracture risk during long-term treatment.

As I'm probably the third person to show this slide design, I'd like to illustrate two key points. That is, patients had a prior exposure of alendronate during FIT and the post-FIT open label treatment of approximately five years prior to randomization into FLEX. Of the 1,099 patients who agreed to participate in FLEX, patients were randomized to placebo, alendronate 5 or 10 milligrams for five more years. Results of almost all evaluations are similar between the 5- and 10-milligram doses; therefore, results of both alendronate groups are pooled and compared to placebo.

During FIT, shown on the left, there was an increase in total hip BMD of about 3 and a half percent. In FLEX, there was a small, nonsignificant decrease with continued treatment, but in contrast, those switched to placebo

experienced the loss of BMD back to the original FIT baseline. The principal fracture outcome in FLEX was shown here. That is, clinical vertebral fracture risk was reduced by 55 percent, while there was no significant effect on the risk of either vertebral morphometric fractures or nonvertebral fractures.

FIT and FLEX enrolled a broad spectrum of patients who were a mix of osteoporotic and osteopenic postmenopausal women. If we were doing this study again today, possibly two-thirds of the patients enrolled in the clinical fracture arm of FIT would not be enrolled because they had a relatively high BMD. The study started in 1992 and was done by the standards of the day.

But what we need to pay attention to now is in a post hoc analysis that explored the relationship between hip/neck BMD at the start of FLEX and the risk of nonvertebral fractures during FLEX, the numbers of patients in each BMD category are shown in the bars. Note that I'm illustrating what Dr. Schwartz illustrated in the publication,

hip/neck BMD at the start of FLEX and not total hip BMD. I believe Dr. Bauer used total hip BMD in the illustrations.

In FLEX participants with a femoral neck BMD T-score greater than minus 2, there was no reduction in the risk of nonvertebral fractures with alendronate. However, a significant 50 percent reduction in the risk of nonvertebral fractures was observed in those with a BMD T-score less than minus 2.5. When a T-score of less than minus 2 was used to define the subgroup, shown in the bars to the far right, a 39 percent nonvertebral fracture risk reduction was observed.

In the Merck clinical trials' experience, there were no reports of osteonecrosis of the jaw in any clinical study of alendronate conducted by Merck. There were two reports of esophageal cancer after short durations of treatment, with no reports during longer treatment.

For atypical subtrochanteric and diaphyseal femur fractures, the location of femur fractures was evaluated in FIT and FLEX. Subtrochanteric and

diaphyseal femur fractures were rare and occurred in both the alendronate- and placebo-treated patients. The location of femur fractures in FIT was evaluated using radiologist reports of the fractures. Fractures could be accurately identified as being the subtrochanteric and diaphyseal femur; however, radiographs were not available to review for additional atypical features.

One patient in each treatment group had a subtrochanteric or shaft femur fracture, illustrated by the bars on the far right. These fractures were rare, with hip fractures about 40-fold more common than subtrochanteric fractures.

Three patients experienced subtrochanteric or diaphyseal femur fracture in FLEX, shown in the two far right boxes. No increase in risk was observed in patients treated with alendronate.

This final slide provides our perspective on restricting the duration of use and drug holiday. In the case of alendronate, 10-year clinical trial data support a favorable benefit to risk profile in

osteoporotic patients who remain at risk of fracture and require long-term treatment.

That's not to say that all patients require long-term treatment. A drug holiday may be considered for patients who are no longer considered to be at sufficiently high fracture risk. However, neither restricting the duration of use nor implementing a drug holiday is likely to be beneficial for patients who remain at sufficiently high fracture risk and require long-term treatment.

In patients who require long-term treatment, interruption in treatment would result in increased bone turnover within a month, loss of BMD acquired during treatment over several years, and increased fracture risk versus continued treatment.

There are insufficient data to predict the effect of interruption of treatment on rare adverse events. Thus, each patient has unique risks of bone loss, fracture, potential adverse drug effects, as well as response to prior therapy. And each patient on bisphosphonate therapy should be reevaluated on a periodic basis to determine the

need for continued therapy.

Thank you very much for the opportunity to present our data and opinions.

[Applause.]

DR. CARSON: Thank you, Dr. Santora. Appreciate your also keeping the time so exactly.

Panel members, please write down your questions specific to each speaker, and after all of the sponsors speak, we'll have time to address them individually. Thanks.

The next presentation is by Warner Chilcott, Dr. Matthew Lamb, who's the senior director of regulatory affairs at Warner Chilcott. And I will ask you to introduce Dr. Miller when the time is right.

Sponsor Presentation - Matthew Lamb

DR. LAMB: Will do. Thank you. And thank you, Dr. Santora.

Good morning. I'm Matthew Lamb, senior director of drug regulatory affairs at Warner Chilcott. On behalf of the company, I want to thank the committee members, Madam Chair, as well

as FDA for the opportunity to present our long-term data on risedronate, specifically focusing on the issue of drug holiday.

We are very pleased to have with us Dr. Paul Miller, distinguished clinical professor of medicine from the University of Colorado Health Sciences System. For over 40 years, Dr. Miller has been involved in bisphosphonate clinical research while also maintaining a very active clinical practice, where almost on a daily basis he needs to consider much of what we're going to be discussing today. After my brief introduction, Dr. Miller will spend a few minutes presenting information on the concept of drug holidays.

We are also very pleased to have with us Dr. Graham Russell, professor of musculoskeletal pharmacology at the University of Oxford and Sheffield University. Professor Russell was involved in the initial discovery of the biologic activity of bisphosphonates and has been instrumental in the unraveling of the bisphosphonate mechanism of action.

In addition to Dr. Miller and Dr. Russell, we also have Dr. Herman Ellman, Dr. Ralph Bobo, and myself who will be available for questions if the panel has any.

In October 2009, Warner Chilcott acquired Procter & Gamble's global prescription pharmaceutical business, which included the bisphosphonate, risedronate sodium. We currently have two products in the market that contain risedronate sodium, Actonel, which is an immediate-release film-coated tablet that was approved in 2000 for the treatment and prevention of postmenopausal osteoporosis, and Atelvia, which is a delayed-release enteric-coated tablet that was approved in October of 2010 for the treatment of postmenopausal osteoporosis. One distinguishing characteristic of Atelvia is that it's to be taken immediately following breakfast and not under fasting conditions, as is the case for the other oral bisphosphonates.

The efficacy and the safety data that was summarized in our background package came from the

following two data sources: first, our clinical trials experience in postmenopausal osteoporosis, where we had 21,000 patients in over 20 clinical studies who were treated for up to 10 years, with a majority of patients being treated for up to three years.

Additionally, as has been commented on in some of the earlier presentations, we do have treatment discontinuation as well as interruption that has been evaluated for one year following both two years, three years, and seven years of continuous treatment. The other data source comes from our postmarketing experience, where we have an estimated patient exposure of approximately 27.7 million patient-years. And that's across all indications.

In response to the FDA questions that have been raised concerning the long-term use of bisphosphonates as well as the issue of and the potential need for drug holiday, Warner Chilcott has concluded the following.

One, risedronate has established long-term

anti-fracture efficacy at both vertebral and nonvertebral sites, which include data from a five-year placebo-controlled trial.

Two, overall benefit/risk ratio for the long-term use of risedronate remains positive. No causal relationship to the use of risedronate has been established for osteonecrosis of the jaw, esophageal cancer, or atypical fracture.

There is insufficient data to support an a priori drug holiday at a specific time point and for a specific duration for all patients. We believe that the need for intermittent use and/or drug holiday may be evaluated on an individual patient basis by the physician and the patient, taking into account risk factors, disease status, treatment history, and future treatment goals.

Finally, FDA-approved labeling provides current and appropriate safety information and recommendations to physicians and patients, including the recommendation that physicians periodically reevaluate the need for continued risedronate treatment.

The specific efficacy data and safety data that support all of these various conclusions have been summarized in our background package, and the remainder of the presentation is going to be coming from Dr. Paul Miller, who's really going to focus in on risedronate and specific points about drug holiday.

Dr. Miller.

Sponsor Presentation - Paul Miller

DR. PAUL MILLER: Thank you, Dr. Lamb and ladies and gentlemen, Dr. Carson, for the opportunity to present my perspective on this issue of bisphosphonates in this important committee meeting, to be able to provide practicing clinicians with some better understanding of what the science and the agency feels about this question of drug holidays.

Having had the privilege of living through the development of bisphosphonates and active clinical trial work and active clinical practice for 40 years now, I have a unique perspective on the terminology and how it evolved to this day in

2011.

When bisphosphonates were first launched, this term "drug holiday" was never a topic of discussion, predominately because of the fact that it was new and we didn't treat a lot of women in their 50s or early 60s with bisphosphonates. We treated sicker women in their 70s and 80s.

Then July 9, 2002 came, and that was the publication in JAMA of the Women's Health Initiative. And as a result of that, millions of women discontinued hormonal replacement therapy and flooded our offices, literally, with questions about osteoporosis because they were concerned. Their mothers, their grandmothers, they had bone densities done, and we found that they had this T-score of minus 2.5, and the only available agent that we had for concerned patients for intervention were bisphosphonates.

The next step in the evolution of this terminology was the better understanding of the pharmacology of bisphosphonates, much of the great work that's been done over the last 40 years by

Professor Herbie Fleisch, Professor Russell, and others noted.

Bisphosphonates are unique. They are not metabolized, the only drug in clinical medicine that is not metabolized. They get bound to bone. They get buried in bone. They get recycled. They come back into the bloodstream. And a proportion of that that goes back into the bloodstream is eliminated in the urine unchanged, and proportion goes to another bone site, where it acts the same as if you're taking the pill.

So with this unique understanding of this long effect of bisphosphonates' maintenance of biological activity, then came the FLEX data. And you've heard much about FLEX. And FLEX gave us assurance in clinical practice that there were groups of people who we could think about taking off, particularly the people who didn't have a prior fracture or people with T-scores that were better than minus 2.5 at the hip. And in that next period of being taken off, particularly with alendronate, after five years of use, they did

pretty well. And that provided a lot of discussion about this group of people that we could now safely take off or another group of people that we may not be safe to take off.

Then came FRAX. And FRAX told us in hindsight that a T is not a T is not a T is not a T, and that we should consider other clinical risk factors in assessing fracture risk in untreated people. And FRAX told us that in hindsight, there were groups of people, younger, who had osteoporosis at the hip or the spine, but with other clinical risk factors not being present, had such a low risk that in hindsight might not need to be treated at all.

As I go around the country, the importance of this committee, I cannot overestimate this and overstate the issue because this is not a standard of care in what we do, and we need some guidance in this direction.

Other considerations about efficacy related to interruption that we've all discussed here, and we will continue to discuss: Do we know enough

1 concerning the persistence or loss of effect upon
2 interruption? We need more data here. The
3 pharmacological activity of bisphosphonates will
4 persist because of drug reservoir in bone and
5 recycling of bisphosphonates. And this activity
6 will diminish to varying degrees over time. And
7 not only will it diminish to varying degrees over
8 time among different bisphosphonates, but even
9 within the same bisphosphonate it will vary among
10 patients; because unlike clinical trial patients,
11 patients in the real world of practice don't follow
12 the same rules. They often are noncompliant. They
13 often don't absorb it as well because of comorbid
14 diseases. And so their total body pool, their
15 reservoir, after five or six years of a
16 bisphosphonate may not be the same from one patient
17 to the next because of these variabilities.
18 So we can't trust whether or not a five-
19 year, or a three-year, or six-year period will
20 behave the same, even with the same bisphosphonate.
21 Dr. Cooper asked the question to Dr. Bauer
22 earlier, are there pharmacological differences

among bisphosphonates? And the answer is yes, there are, in head-to-head data. And, in fact, there's some wonderful science in this regard that I will show in the next two slides. But to reiterate Dr. Bauer's point, there have never been head-to-head data comparing fracture outcomes among bisphosphonates, nor have there been head-to-head data of what happens when you take patients off bisphosphonates in head-to-head trials among the bisphosphonates.

The in vitro data shows this hierarchy of inhibition or affinity for bone surface. Bisphosphonates work two ways, a physical chemical mechanism and a cellular mechanism. The physical chemical mechanism is that is stabilizes the bone surface by binding to the calcium-phosphorus surface. And you can see this hierarchy of affinity for the surface, with zoledronic acid having the highest affinity. And some of these affinity differences may explain in part the ability to give longer dosing-free intervals.

In addition, at the cellular activity, the

enzyme in the osteoclasts, farnesyl pyrophosphate synthase, is inhibited to different degrees by different bisphosphonates. So in this hierarchy, going from the left to right, you'll see that zoledronic acid inhibits this enzyme the greatest, then risedronate, then ibandronate, and on right-hand side, this correlates to the amount of bone resorption and calcium release from bone from a rat calvarial model. So there are differences, certainly, physical chemically, in that regard.

The long-term risedronate data that I'll show you here to try to tie this story together -- you've seen some of this data so it won't take me very long to go through it. This is the 7-year data. This is being published now as we're here today; this will be in the November 2000 [sic] issue of the JCEM. The first author is Professor Richard Eastell and colleagues.

What this data fundamentally shows is that continuation of risedronate through seven years maintains suppression of bone remodeling. You'll see that it doesn't go below that, like it doesn't

with all bisphosphonates. There's some type of internal regulation that prevents bone suppression from going lower despite continual administration of the bisphosphonate.

But the point here is that when you stop it in year 8, in the off period, even with seven years of use, the biochemical marker of bone resorption, the NTx, rises abruptly, even within six months, to match that of placebo. So long-term use is still associated with rapid reversal, as assessed by markers of bone resorption.

This is the -- in that same population, this is the fracture data. The fracture data through seven years, shown in the red, 0 to 3, 4 to 5, and 6 and 7, the fracture data is maintained. In fact, there's a suggestion that there's a trend, that it gets better over time, although the numbers are small. But certainly this is persistence of effect through seven years of administration.

This is Nelson Watts' slide from the North American registration trial of risedronate. And in this trial, the North American group received three

1 years of risedronate or placebo and then were
2 stopped. And when it was stopped, on the left-hand
3 side, the NTx came back close to the placebo group,
4 abruptly went up. And on the right-hand side, the
5 femoral neck BMD dropped abruptly as well, within
6 one year after three years of exposure.
7 In that same population, as shown on this
8 slide, is the fracture data. And in the patients
9 taken off therapy and followed in year 4, the
10 fracture benefit is no longer evident in the former
11 risedronate-treated patients compared to former
12 placebo-treated patients. Whether you look at new
13 vertebral fractures, the percentages, or the
14 absolute numbers are the same, or the nonvertebral
15 fractures. So consistent with the rise in NTx and
16 the drop in BMD is the loss of the fracture
17 protection in one year.
18 Bone mineral density as a primary endpoint,
19 and changes in biochemical markers of bone turnover
20 as secondary endpoints, have been accepted by this
21 agency for registration of the alternative dosing
22 bisphosphonate therapies. The weekly

bisphosphonates, the monthly bisphosphonates, the quarterly bisphosphonates, have all been approved not on the basis of fracture data but on the basis of the fact that the surrogate markers change to the same degree as the fracture-proven daily dose.

There's an implication there. So that interruption of risedronate therapy results in rapid reversal of suppression of bone turnover markers within one year and a decline in BMD at some skeletal sites. And it appears, although the sample sizes are small, that continued risedronate therapy appears to provide continued fracture benefit.

The data suggest that a fall in BMD and an increase in bone turnover markers are associated with the return of fracture risk soon after interrupting risedronate therapy.

In conclusion --

DR. CARSON: Dr. Lamb, you only have about 30 more seconds.

DR. LAMB: Thank you very much.

In conclusion, bisphosphonate drug holidays

1 have become a hot topic due to the special
2 properties of bisphosphonates and FRAX in
3 hindsight, and the potential safety concerns with
4 long-term use.
5 The final slide here shows that calculating
6 FRAX, a 70-year-old woman with a femoral neck T-
7 score of minus 3 has a 25 percent 10-year risk
8 untreated of a major fracture, which is reduced by
9 bisphosphonates to about 50 percent. That is a
10 tremendous benefit when put in the context of these
11 very rare risks of these unestablished events.
12 FDA-approved labeling, we need to be
13 cautious in considering drug holidays in high-risk
14 patients, prior fragility fracture, older women
15 with osteoporosis of the hip, or high-risk scores.
16 And if drug therapy is interrupted, we should
17 discuss and consider that clinicians monitor, with
18 some form of monitoring tools, BMD and bone
19 turnover markers to assess the loss of effect on
20 bone turnover.
21 With that, I thank you for the privilege of
22 having me.

[Applause.]

DR. CARSON: Thank you.

Dr. Joseph Kohles, who's the international medical leader for Boniva at Hoffman-LaRoche, Incorporated, will be discussing that drug.

Sponsor Presentation - Joseph Kohles

DR. KOHLES: Good morning, Madam Chairwoman, distinguished members of the panel. Thank you for giving us the opportunity to present to you today. My name is Joseph Kohles. I'm the international medical leader for Boniva. I'm a former medical director with Roche, and am now a consultant with the company.

So we were asked two questions by the FDA. The first is around the long-term use, and the second was around drug holiday. We're going to specifically answer those questions, but I wanted to provide the evidence in support of our opinions in this presentation. So the evidence we would like to present is around our pivotal fracture data, long-term extension data, and safety data overall.

Boniva had a very robust clinical development program. There was over 11,000 patients across 38 different trials. And it's unique in that there was an IV and an oral formulation developed in parallel at the same time. A wide range of doses were tested in order to arrive at the optimal dose and duration of treatment.

The core of the clinical development program was the bone fracture trial. This was the trial that compared the 2.5-milligram daily dose to that of placebo. This was a three-year study with a primary endpoint of new morphometric vertebral fractures at three years. The study demonstrated robust efficacy with Boniva. There is a 50 percent relative risk reduction in new vertebral fractures at years 2 and 3, and this is what led to the approval in the U.S. and the E.U. of Boniva.

The patients prefer less frequent dosing. We know that patients are more compliant and persistent and adherent if they don't have to take as much medication. So for this reason, we

1 developed a monthly and a quarterly dose of Boniva.
2 As was previously mentioned, we used the bridging
3 concept, which was utilized by other
4 bisphosphonates, to bridge back to the 2.5-
5 milligram daily dose, which is where the fracture
6 efficacy was established.
7 So we tested three different monthly doses.
8 The one of most importance is the one 50-milligram
9 monthly. And, again, that was compared back to the
10 2.5-milligram daily. In the IV formulations, we
11 tried two different formulations, the primary of
12 which was the 3-milligram quarterly compared back
13 again to the 2.5 daily. These were both 2-year
14 trials with a primary endpoint of lumbar spine.
15 So the goal of these bridging trials was to
16 show that the quarterly IV dose and the monthly
17 dose were at least as good as the daily dose. But
18 the study actually showed that they in some manners
19 were superior. You can see by this slide, in the
20 upper left-hand corner at the lumbar spine, the
21 blue bar is Boniva 150 monthly, and you can see
22 that there's a superior improvement in lumbar spine

bone mineral density. Similarly, with the green on the right, the DIVA trial, that's the IV quarterly. It was statistically superior to the daily. Results were similar in total hip BMD in that there were improvements in both the monthly dose and the quarterly IV dose over the daily doses.

In order to establish the longer term efficacy and safety of Boniva, we extended these bridging trials out, and you can see by this diagram. The initial trial was two years. The long-term extension was three additional years. Those patients who were on 2.5-milligram daily or 50/50 were re-randomized to receive 100 milligrams monthly, or 150. Those patients who were on the 100 milligrams or the 150 were continued on therapy for an additional three years. So, in total, those patients were on therapy for five years. There's a similar design in the IV trial as well.

So the results from this trial show -- and this is first the bone turnover marker, P1NP. You can see there's a suppression down to premenopausal levels of suppression, and that is maintained

1 throughout the five-year period of treatment.
2 Similar with the IV dose; there's a suppression
3 down to premenopausal levels, and then a
4 maintenance of that effect throughout the five-year
5 period.
6 So this is the primary endpoint of the
7 extension study. Those bone turnover suppressions
8 relate back to improvements in bone mineral
9 density. So you can see that after the initial
10 treatment period, which is the upper left-hand
11 corner before the dotted line, there is that
12 initial improvement in BMD which we showed in the
13 initial trial. And then in the extension, you can
14 see a continued increase in lumbar spine going out
15 through the five-year period. The same was true
16 for the IV dose. With regard to total hip, again
17 you can see the initial improvement in total hip
18 BMD at two years. And then there's a maintenance
19 of that BMD throughout the five-year period.
20 So MOBILE and DIVA were not fracture trials.
21 However, they did collect fracture information as
22 adverse events, and any fractures collected were

confirmed radiographically.

So we looked at the fracture data from those trials, from the MOBILE and DIVA. We pooled together the relevant doses of 150, 2 milligrams, and 3 milligrams, and looked at it over time. And what we saw is that there's a relatively low all clinical fracture rate that is consistent throughout the five-year period. The same is true for nonvertebral fractures. It's low and consistent throughout the five-year period. We were comforted by the fact that there was no drastic increase in fracture rates at years 4 or 5, so it was consistent throughout the entire period.

With any bone-altering medication, it's important to assess the quality of bone after treatment. We did this by bone biopsy cores, and we took samples in several different trials, the BONE trial, the DIVA, and the DIVA long-term extension. And you can see by these numbers we have quite a few biopsies, all the way up to five years. Many of them were paired. But, overall, what we showed is that the culmination of this

1 data -- and you can see the references there. The
2 culmination of this data shows that newly formed
3 bone retained its normal lamellar structure. There
4 was no woven bone, no marrow fibrosis. And from a
5 quantitative standpoint, there was no impairment of
6 mineralization, and the bone remodeling occurred at
7 premenopausal levels. So this gave us comfort that
8 the patients maintained normal bone quality
9 throughout the five-year period.
10 So to summarize the evidence we just showed,
11 the oral monthly and IV quarterly dose were shown
12 to be superior to daily. BMD, on the long term,
13 either continued to increase or was maintained
14 throughout the five-year period. That was low
15 clinical fracture rates overall, and those fracture
16 rates were maintained. And the biopsy data showed
17 normal bone quality throughout the period.
18 Next, we'll look at safety. First, from an
19 overall safety standpoint, the safety of Boniva is
20 well-established and was first established in the
21 BONE trial with a 2.5-milligram dose. And it was
22 well-tolerated and, overall, similar to placebo.

When we look at the 150- and the 3-milligram dose, we see that it's very similar to the 2.5 daily dose with regard to overall adverse events. And we do not see any change in the safety profile as we extended the period of treatment out throughout five years.

But in order to fully assess the safety of Boniva, we wanted to look more closely at three specific events, atypical fracture, ONJ, and esophageal cancer. So we looked at all the data sources available to us: our clinical development program, postmarketing, spontaneous reports, and the literature. And we did a thorough review and adjudication of all the cases collected through those data sources by an internal team of physicians.

This is the results of that analysis. This is from the clinical development program. You can see that there were over 11,000 patients on Boniva. Sixty-seven of those had a hip or femur fracture. Five were in the correct region of subtrochanteric or femoral shaft, but none ultimately met the

criteria for atypical fracture.

When looking at placebo, there were 2,000 patients on placebo. Twenty had a hip or femur fracture. One was in the correct region, but that one ultimately did not meet the criteria. Based on this evidence, we did not see an increased incidence of atypical fracture in our clinical development program.

Looking at spontaneous reports and literature, as previously mentioned, this data is problematic overall, but we're presenting it in an effort of transparency. There was 172 hip and femur fractures identified in the literature and in spontaneous reports, 41 of which were in the correct region, subtrochanteric or femoral shaft. Eight ultimately met all the criteria for atypical fractures. Thirty-three were features of a tibia unknown.

Moving on to ONJ, there were no cases of ONJ reported in the clinical development program, again, of more than 11,000 patients. When we look at spontaneous reports, there was 176 potential

cases. Forty-nine had necrotic bone, and 34 ultimately met the criteria for adjudication for ONJ.

These events are serious when they happen to these patients. Thankfully, they are rare. These are the crude reporting rates that we obtained. This is just from our spontaneous data, so this is a very crude estimate. Out of the eight patients -- out of our overall exposure, we see about .3 per 1 million patients for atypical fractures. For ONJ, it's 2.1 per 1 million patients.

Looking at esophageal cancer, we had two cases in the clinical development program, which led to an incident rate of 7.4 per 100,000 patient-years. That's compared to a background rate, as reported in the FDA briefing document, of 11.2 per 100,000 patient-years. There was also six spontaneous reports in our database.

So, again, we take these cases very seriously. We take these events very seriously. And we took steps to manage the risk overall. The

first was the full case adjudication, which I previously presented to you. The second is that we updated the package insert with information on ONJ and atypical fractures. We implemented a medication guide that's handed out with every prescription for the patient to have information about these events. And we also instituted a guided questionnaire so that any atypical or ONJ suspected adverse event that comes into our database automatically gets asked a series of question to obtain as much information about those cases as possible.

So with regard to question number 1 asked by the FDA around long-term use, we believe that Boniva treatment for up to five years is safe and effective, and the benefit/risk profile for the drug remains favorable over this time.

With regard to the second question of drug holiday, it's important to look at a few different factors. The first is what happens when a patient comes off treatment. So you can see on the top graph -- this is from Raven and group, and it shows

the orange bar on the top is the 2.5-milligram daily dose. And this is for lumbar spine on the top graph. And you can see that in the first 12 months where patients are on treatment, there's an increase in lumbar spine bone mineral density. After 12 months patients came off treatment, and you can see there's a decrease in bone mineral density after that time.

Correspondingly, there's a suppression -- on the bottom graph, there's a suppression in bone turnover when patients are on treatment -- this is urinary CTX -- and that suppression is maintained throughout the treatment period. However, when patients come off treatment -- and this is came off for a year -- you can see that there's a return in the urinary CTX.

Another thing that needs to be considered is the risk factors associated with osteoporosis. There are a multitude of different risk factors: age, prior fracture, family history, more environmental effects like smoking and alcohol intake. And so this means that there's a multitude

1 of patients that will present to any different
2 clinician.
3 So for these reasons, it's our opinion that
4 the need for continued therapy should be
5 reevaluated periodically, and a drug holiday may be
6 appropriate for some patients. But any
7 interruption of treatment should be based on the
8 individual risk/benefit assessment, and the
9 physician is in the best position to make that
10 determination overall.
11 I want to thank you for your time.
12 [Applause.]
13 DR. CARSON: Thank you, and I appreciate
14 your attention to the time.
15 Our final sponsor speaker is Dr. Christina
16 Bucci-Rechtweg, the global program medical director
17 for Novartis Pharmaceuticals Corporation. She'll
18 be discussing Novartis.
19 **Sponsor Presentation - Christina Bucci-Rechtweg**
20 DR. BUCCI-RECHTWEG: Good morning. My name
21 is Christina Bucci-Rechtweg, and I am an employee
22 of Novartis Pharmaceuticals. I'll be outlining for

1 you today that data from within the Reclast
2 clinical development program can provide insight
3 into the use of Reclast in the long-term management
4 of osteoporosis beyond three years.
5 You've heard presentations from the three
6 previous sponsors related to oral bisphosphonates.
7 I'll be speaking today about the IV bisphosphonate
8 used in the treatment of osteoporosis.
9 Reclast is administered as a 5-milligram IV
10 injection of zoledronic acid and was developed to
11 address issues related to poor oral compliance with
12 oral bisphosphonates. As has been mentioned, it
13 was first approved for use in 2007, and amongst its
14 indications is indicated in the U.S. for the
15 treatment and prevention of postmenopausal
16 osteoporosis, which is what I will focus on today.
17 Zoledronic acid, the active ingredient in
18 Reclast, is also approved as Zometa for use in
19 patients with advanced cancer in bone, in patients
20 with different comorbidities and different
21 confounding factors, and utilizing a different dose
22 and dose regimen. Therefore, Zometa will not be

the focus of today's presentation.

The data that I will discuss today is specific to three trials within our development program, the first being the pivotal fracture trial in women with postmenopausal osteoporosis. The second is the three-year extension study, and the third the recurrent fracture trial in men and women with an incident hip fracture.

In the pivotal fracture trial in women with postmenopausal osteoporosis, this is the only bisphosphonate study that's a registration trial that was powered adequately to assess both new morphometric vertebral fracture and hip fracture as co-primary efficacy endpoints. At the end of this three-year study, women randomized to receive three annual infusions of zoledronic acid, or Reclast, showed statistically significant reductions in risk of both new morphometric vertebral fractures and hip fractures.

In the recurrent fracture trial, which was a trial of men and women with incident hip fracture within 90 days of randomization, the primary

efficacy endpoint was clinical fractures. Patients with incident hip fracture have a two and a half-fold higher incidence of subsequent fracture, and therefore this endpoint is very specific to this important fracture type.

At the end of the study, men and women randomized to receive annual infusions of Reclast therapy had a statistically significant reduction in clinical fractures at the end of the trial. For the other fracture endpoints, including nonvertebral fracture and clinical vertebral fracture, similar findings were found.

With hip fracture, there was only one hip to break since the patients were randomized with an incident fracture. And while this finding was not statistically significant, the magnitude of change was similar to what had been observed in the pivotal fracture trial.

Importantly, in patients with hip fracture, there is an excess risk for mortality that's been observed in literature -- excuse me, reported in literature -- out to five years following hip

fracture. In this randomized controlled trial, patients who received an annual infusion of Reclast therapy showed a statistically significant reduction in the three-year cumulative risk for all-cause mortality at the three-year time point.

I'll now focus on the extension data. As has been pointed out previously, the extension data took women who had been randomized to receive three years of active therapy during the core trial who were re-randomized to either receive an additional three years of zoledronic acid or to be discontinued from therapy.

For women in the first three years of the study of the pivotal fracture trial who received annual infusions of Reclast, there was a significant increase in the femoral neck bone mineral density. The primary efficacy endpoint, as has been noted in the extension trial, was the percentage change in femoral neck bone mineral density from year 6 to year 3 of the extension trial.

For those patients who were re-randomized,

1 women who continued on therapy, shown in green,
2 showed a slight increase in maintenance of the
3 effect on bone mineral density at the end of the
4 trial; whereas those women who were discontinued,
5 in red, had a modest decrease in their bone mineral
6 density at the end of the study.
7 For markers of bone turnover, specific to
8 bone turnover markers for formation, what was seen
9 in the first three years of the study during the
10 pivotal fracture trial was a classical response to
11 Reclast therapy, where there was a robust response,
12 and that finding over time is maintained to the
13 three-year time point.
14 For women who continued on therapy, shown
15 again in green, this suppression remained out
16 through the six-year time point. And for those
17 patients who discontinued from therapy, there was
18 a modest increase back within the premenopausal
19 reference range.
20 But the goal of therapy for osteoporosis, as
21 you've heard, is the prevention of fracture. I'll
22 remind you that in the core pivotal fracture trial,

patients who received no active therapy had a 10.9 percent incidence of new morphometric vertebral fractures, whereas those patients who received active therapy had a significant reduction in risk for morphometric vertebral fracture.

In patients who continued on therapy, that reduction in risk for morphometric vertebral fracture was maintained out at the six-year time point; whereas those patients who discontinued from therapy, shown in red, had a loss of that effect at the end of the three-year extension.

So to better understand who might be the patients at risk for fracture if therapy is discontinued, Felicia Cosman and colleagues conducted a post hoc analysis of the extension study, which has not been yet presented in the public domain and will be presented next week at the American Society for Bone and Mineral Research.

The objectives of this post hoc analysis were first to identify predictors of both high and low risk for vertebral fracture and to determine whether the observed treatment effect of continued

therapy on vertebral fracture is consistent to cross those predictors for risk.

The methods that were utilized for this analysis included a logistic regression analysis in the discontinuation arm, or the Z3P3 arm. The variables that were assessed as part of this model included age, hip bone mineral density, P1NP, and prevalent vertebral fracture at the extension baseline. Additionally, incident vertebral and nonvertebral fracture, weight loss, and the percentage change in hip bone mineral density during the core pivotal fracture trial were also assessed.

Secondly, an analysis of treatment effects comparing those patients who continued on therapy versus those patients who discontinued from therapy in subgroups defined by significant predictors of risk for vertebral fracture was conducted. And then finally, a parallel analysis for nonvertebral fractures using Cox proportional hazards models was assessed and will be only briefly discussed in this presentation.

Once all the variables were assessed in the logistic regression model, those predictors for risk of vertebral fracture and the patients who discontinued for therapy that were statistically significant included a persistently low femoral neck bone mineral density T-score and a persistently low total hip bone mineral density T-score at the extension baseline. In addition, incident vertebral fracture while on therapy during the core study was also significant.

Literature has reported frequently that prevalent vertebral fracture is a very important predictor for risk of future fracture. And in this post hoc analysis, while there was a twofold increase in risk utilizing the odds ratio analysis, this was not significant.

However, in the parallel analysis of patients with nonvertebral fractures, looking at predictors for risk, patients with prevalent vertebral fracture at the extension baseline showed a highly significant predictive risk for nonvertebral fracture if there in fact was a

prevalent vertebral fracture at the extension baseline. Therefore, the authors have concluded that prevalent vertebral fracture should be considered as an important predictor for risk for vertebral fracture.

Now, there's a second component to this analysis, and that was to assess treatment effects in subgroups based on their predictors for risk in those patients who continued from therapy versus those patients who discontinued from therapy. And for those predictors of risk that I just outlined, the test is significant.

What we saw is that regardless of subgroup, high risk or low-risk, we saw that the mean odds ratio fell to the left of 1 and therefore favored the continued treatment with zoledronic acid. However, this sample is a small sample, and there's a long tail on these 95 percent confidence intervals. Therefore, the treatment by subgroup interactions are also not significant.

But more so and more importantly, this helps us to identify that for patients who may be in low-

1 risk categories such as a bone mineral density T-
2 score that's no longer osteoporotic at the
3 extension baseline, there may be a component of
4 these patients who could discontinue from therapy.
5 Now, when looking at the actual incidence
6 rates, what we saw is that the incident of
7 vertebral fracture was higher in those patients who
8 discontinued from therapy. And maybe more so
9 importantly, looking at the numbers needed to
10 treat, in those patients who were considered to
11 still be within the high-risk groups, such as the
12 osteoporotic bone mineral density, or with an
13 incident vertebral fracture while on therapy, or
14 with a prevalent vertebral fracture, if you're in
15 the high-risk group, your number needed to treat
16 was lower, oftentimes multiple-fold, than those
17 patients in the low-risk treatment groups -- excuse
18 me, in the low-risk groups.
19 So now I'm going to transition my discussion
20 to the safety. As there were no esophageal cancer
21 events in the Reclast database, and as Reclast is
22 administered as a parenteral infusion, I will focus

this presentation on skeletal events of interest.

First I'll focus on bone biopsies, as structure is an important part of this discussion about the long-term use. In both the pivotal fracture trial and the extension study, qualitative and quantitative histomorphometry and micro CT assessments have been conducted.

Within the pivotal fracture trial, annual dosing for three years resulted in a preservation of bone structure and material properties without any evidence of adynamic bone. While in the pivotal fracture trial extension there were only five specimens to analyze as part of this assessment, all contained trabecular double label.

To look specifically at maxillofacial safety events, it's important to remember that Reclast, being the most recent bisphosphonate to the market, had the benefit of looking at available safety issues or mechanism issues that could affect the product. Therefore, this is the only bisphosphonate to have incorporated a prospective program-wide event adjudication for events of

special interest, including osteonecrosis of the jaw.

This prospective adjudication included the incorporation of an external blinded expert committee, who set a charter that defined 60 predefined MedDRA search terms looking for adverse and serious adverse events of special interest that would routinely go into the database and pull up as trials were ongoing.

The definition that was utilized as part of this assessment was exposed bone with delayed healing long despite six weeks of appropriate medical care, which is a more conservative definition than that which is currently used.

During our program-wide adjudication of the entire Reclast clinical trials registration program, four cases potentially consistent with osteonecrosis of the jaw were identified, all of which were treated with debridement and/or antibiotic and resolved. Important to note is that as part of this adjudication, only one of these events was reported as osteonecrosis of the jaw.

In addition, it's important to note that one of the events occurred in a patient who had never received Reclast therapy and in fact received placebo.

Within our postmarketing experience of over 2.3 million patient-years of exposure, our safety database has been routinely queried, and the reporting rate is 4.5 per 100,000 patient-years. Fifty-eight percent of the cases have been reported with one or more risk factor, including prior use of other bisphosphonates, both oral and IV, and only 21 percent of the cases within this database have been reported with exposed jawbone. The rate that's been identified within our postmarketing surveillance system is consistent with the risk associated with the oral bisphosphonate literature.

Now, to turn to the more recent event of interest, I'll talk about atypical fracture. Within our clinical trials program, no atypical fractures have been reported. In cooperation with the FDA and the EMA, we have conducted an interrogation of our clinical trials database looking for terms of hip, femur, and femoral neck

fracture, and reviewed them for consistency with atypical fracture.

As part of this review, five unconfirmed events in the area of interest were identified, including three patients on Reclast, but importantly, two patients with placebo. As the radiographs were not available to assess these patients, these events cannot be confirmed.

Within our postmarketing surveillance, a similar database query has been conducted. Reports of subtrochanteric, diaphyseal, and atypical femur fractures cannot be confirmed, though, to include the major features, as, unfortunately, as part of our postmarketing surveillance, it's very difficult to obtain the nature of the preceding trauma and radiographs for review; though to address this, we do estimate, based on the number of events that we have, a reporting rate of .6 per 100,000 patient-years.

In summary, the benefit/risk of Reclast 5 milligrams IV during long-term treatment, long-term treatment being beyond three years, is

consistent with the profile that's been established in our registration trials program. The clinical trial evidence of a clinically meaningful reduction in fracture risk with Reclast has been identified.

In addition, the number needed to treat to prevent vertebral fractures is low in our three-year study, and in the three-year extension study is 32. This correlates in the pivotal fracture trial to 2500 vertebral fractures, reduced, in 100,000 patient-years.

The number needed to treat to prevent a hip fracture has been identified in the pivotal fracture trial to be 91, though the sample within our extension study is too small to make clinical conclusion. And also, very importantly, with hip fracture, there's been identified a 28 percent reduction in all-cause mortality.

While these events of interest are very important and very impactful to patients, in our clinical trials program and postmarketing surveillance, they have been very rarely reported.

Novartis remains committed to ensuring

patient safety. We currently have an ongoing five-year epidemiology study to assess the incidence of rare safety events. In addition, we've worked collaboratively with the agency to ensure that the U.S. prescribing information reflects the most up-to-date information related to identified and potential risks with long-term Reclast therapy from both our clinical trials program and with postmarketing surveillance.

While our six-year data support a positive benefit/risk for long-term Reclast therapy, post hoc analyses have provided us insights into which patients may benefit most from continued treatment beyond three years in addition to those who may be considered for treatment discontinuation for up to three years. Therefore, the decision to continue or interrupt Reclast therapy beyond three years should be made on an individualized patient basis.

Thank you.

[Applause.]

Clarifying Questions to the Presenters

DR. CARSON: Thank you. In the interests of

time, may I just have all the speakers come up to the podiums, and we'll direct questions to you.

While they're doing that, let me apologize to all of you for my rudeness. I failed to introduce our transcriber, Ms. Janet Evans-Watkins. And thank you for helping us today. My mother really did do a better job than that.

Panel, clarifying questions for the presentations by the sponsors? Dr. Erstad?

DR. ERSTAD: This is a question for Dr. Santora.

Would you explain a little more about how you determined a half-life of the alendronate on the surface of the bone? And then along with that, the implication of that relatively short half-life would imply that literally within a few months, that the effectiveness would be gone. And I'm curious if that was your implication behind that.

DR. SANTORA: First, that it's on the surface of bone was established in animal studies. You can't really do that study in people. So the way we determined the half-life is that volunteers,

1 who were postmenopausal women, received a dose of
2 alendronate intravenously, and the alendronate was
3 recovered in their urine at periodic intervals --
4 first daily, weekly, monthly -- out to a year and a
5 half after the last dose of drug. It's not
6 metabolized. It's not excreted in the GI tract.
7 So you know what's in the urine represents what's
8 being cleared from the body.
9 Terminal elimination excretion rate was
10 calculated based on the amount that came out
11 between one year and a year and a half, 18 months.
12 The short-term elimination was determined based on
13 the excretion over a period of two weeks to about
14 six weeks.
15 It's not a specific half-life of exactly 2
16 and a half weeks or exactly five weeks, but it's in
17 that range, 2 and a half to 5 weeks. And based on
18 where we know the drug is in animals in that same
19 period, that's why I said it's definitely in bone
20 and it's on the surface of bone, based on animal
21 studies.
22 DR. CARSON: Dr. Morrato?

DR. MORRATO: My question is also for Dr. Santora. I'm trying to understand and bridge the findings and conclusions across the different presenters of the same data set, the FLEX data. So I was struck by the fact that in the Merck slides, it was emphasized the total hip BMD changes, whereas in the FDA presentation, it was neck and spine BMD curves that were shared that Dr. Bauer concluded that one- to two-year changes in BMD after discontinuation was not associated with fracture risk. And this would be consistent with the Kaplan-Meier time diffraction curves that the FDA did.

So in light of that, I was hoping that you could comment on the clinical importance of hip BMD changes that you presented relative to the neck and spine changes, and particularly in relationship to actual fracture risk.

DR. SANTORA: All right. I showed data on BMD change in total hip and the neck. In fact, it's probably not easy to get the slides back up. But in one study I showed that total hip BMD in the

phase 3 studies went down gradually over time in five years. In FIT, there were several data points shown --

DR. MORRATO: Right. And with regard to FLEX data. Sorry if I wasn't clear.

DR. SANTORA: Oh, with regard to FLEX data. I showed total hip BMD, and I believe Doug Bauer may have shown both sites. The FDA presentation was hip/neck BMD.

So the point is it's heterogeneous. Hip/neck BMD does not decline very much. Total hip BMD does decline back to pretreatment baseline. So it's different depending on which site you look at.

DR. MORRATO: And my question is, do you make a clinical relevance relative to fracture risk or just an observation that you're seeing changes in BMD?

DR. SANTORA: Well, I think the clinical relevance is that BMD is being lost over time. Fracture risk is really derived by looking at the fracture data from FLEX. I showed the FLEX data, based on subgroups, as they were presented by

Dr. Ann Schwartz and the study that was actually conducted by the coordinating center. I believe Doug Bauer showed a similar representation of data using BMD at the start of FLEX as the total hip BMD.

The take-home message is the same. People with relatively high BMD -- for example, greater than minus 2 with the neck, and I believe it's pretty much the same cut with the total hip -- they have low fracture risk, and that fracture risk is not lowered further with continued treatment.

With low BMD at the hip/neck or the hip/trochanter at the start of FLEX -- let's say minus 2.5 or minus 2 for the total hip -- that population of patients does experience a decrease in fractures if they stay on treatment versus if they change to a placebo.

To be honest, I would not want to speak for the FDA in terms of the way their analysis was done. But we used the same database, the FIT database, for FLEX, but the way I presented it, I just used the different BMD site. Hip/neck, Dr.

Bauer referred to total hip.

DR. CARSON: Does FDA want to respond in terms of that? Dr. Whitaker?

DR. WHITAKER: Yes. We chose to use the femoral neck because we were looking at all three studies, and all of the studies did not include total hip. And so to be consistent and to be able to compare between studies as best as we could, that is why we used the femoral neck.

DR. CARSON: Thank you.

Dr. Orza?

DR. ORZA: A quick question for Dr. Santora, which could also be answered by others, and a quick one for Dr. Kohles, same thing. Total number of subgroup analyses that were done and whether or not they were adjusted for multiple tests. And the question for Dr. Kohles is about how you select the subsets that you do the bone quality testing on.

DR. SANTORA: Yes. The subgroup analysis I referred to is the one done in FLEX by Dr. Schwartz. So that subgroup analysis was justified because a statistically significant

interaction was observed between the treatment effect, that is, the outcome being nonvertebral fracture risk.

So because there was a statistically significant interaction between BMD -- this is hip/neck BMD -- and the treatment outcome, which was nonvertebral fractures, the subgroup analysis is justified based on that interaction. There was no further adjustment for multiple comparisons beyond that. But it was a predefined, look for an interaction; then, if you find it, look for what's found in subgroups.

DR. KOHLES: So with regard to the bone biopsies, it was those patients who agreed to be bone biopsied. And I think as Dr. Miller can attest to, not every patient will agree to a bone biopsy; it's a somewhat painful procedure. But that's mainly it. It's institutions that were doing the bone biopsy and patients who agreed.

DR. CARSON: Dr. Winterstein?

DR. WINTERSTEIN: I have a question for Dr. Bucci-Rechtweg. You mentioned at one of your

last slides that there was an ongoing epidemiological study that looks at safety issues. I think since we all would love to have more data, could you give us some more detail on population size, database, prospective/retrospective types of outcomes, things like that?

DR. BUCCI-RECHTWEG: This epidemiology study is a study that's going to be conducted in Scandinavia utilizing the national healthcare databases that are there, looking at anonymized data sets.

The way the study will be set up is looking at three separate cohorts. The first cohort is only classed users. So these are classed users for postmenopausal osteoporosis, male osteoporosis, glucocorticoid-induced osteoporosis. They'll be matched 1-to-1 by propensity scoring to patients who are oral bisphosphonate users, and then 4-to-1 to untreated matched controls.

So this an analysis of the database between 2007 and 2012, and, again, including all users. So we don't have the complete set yet of how many

patients will ultimately be in that study.

Now, it's set up to look at both cardiovascular and skeletal events. For ONJ in particular, this is a rare event, so you need quite a big sample to be able to assess it. For skeletal events such as appendicular fracture, you don't need as big a size. But, again, the difficulty to potentially assess for events such as atypical fracture will come in, ultimately, at the end of the study because to be able to definitively say these are atypical fractures, radiographs are required to review.

DR. CARSON: Dr. Suarez-Almazor, final question.

DR. SUAREZ-ALMAZOR: I have questions for several of the sponsors. Just one? Okay. Well, alendronate -- I'm sorry -- but I guess I'm choosing alendronate because that's one of the ones that we have the most data, with the FLEX trial. And I just had a couple of comments -- or not comments; questions, actually.

But for the data that you have presented, if

I understand correctly, what you have shown that would support continuing use of alendronate is, from the FLEX data in those patients with the BMD less than minus 2.5, hip BMD, a reduction in vertebral fracture, but for the other subgroups, there's no difference.

Is that correct?

DR. SANTORA: Yes. Actually, if you take all patients, regardless of BMD, there is a risk reduction in clinical vertebral fractures by about 50 percent. So there's -- actually, I was just thinking of all the patients. So this is greater than -- could we go to the slide that just illustrates clinical vertebral fractures in the subgroup less than minus 2?

We actually had this as backup because there was no interaction between BMD and clinical vertebral fracture risk reduction. We didn't do a subgroup. We've only prepared data if there were specific questions.

Now, your other question is about nonvertebral fracture risk. That is the site where

we saw -- sorry. Hip/neck BMD was associated with nonvertebral fracture risk reduction. That is there was an interaction with a statistical test. Based on that interaction, we found that people who had a relatively high hip/neck BMD, that is, greater than minus 2, had a low fracture risk, and that fracture risk was not reduced further. So there was no treatment in that group.

If you take the cut point at minus 2.5, that group, despite prior therapy, who had a BMD T-score at the femoral neck less than minus 2.5, there was about a 50 percent reduction in risk. If you take the cut point and set it at minus 2, that group, minus 2 or less at the femoral neck, had a risk reduction of about 39 percent for nonvertebral fractures.

Did I answer your question?

DR. SUAREZ-ALMAZOR: Yes. Okay. So that's in a subgroup.

DR. SANTORA: That's correct.

DR. SUAREZ-ALMAZOR: But, again, when you put it all together, you find possibly an effect,

1 but it's driven by those who have lower bone mass.
2 It's not seen in all of the --
3 DR. SANTORA: No, that's exactly right. And
4 as I mentioned, when we started FIT, we
5 didn't -- that was the years before the WHO set the
6 criteria. So what's really important is how the
7 drug works in people who will be prescribed the
8 drug today. WHO uses a criteria of minus 2.5.
9 Other groups use a criteria of minus 2 or less.
10 But it's all low bone density patients. These
11 days, you wouldn't treat somebody for osteoporosis
12 if their BMD T-score was minus 1.6.
13 So I think we're looking at the patient
14 population that actually receives the drugs today.
15 But you're right, it is post hoc.
16 DR. SUAREZ-ALMAZOR: Okay. And related to
17 that also, there are a couple of pieces of
18 information that were given that to me seem somehow
19 contradictory, although they are related more to
20 the placebo group. On one hand, you're saying that
21 the lower the BMD in the hip, the higher the
22 occurrence of fracture later on. But then there

was also the suggestion that the change in BMD afterwards was not related to the fracture. But what we are trying to do with the bisphosphonate is change that BMD.

So on one hand, you're telling me lower BMD is related to the risk of fracture, but change in that BMD, for the better or for the worse, is not related to the subsequent fracture. So that seems to be contradictory to some degree.

DR. SANTORA: Right. Well, actually, it might at the top level. So if you take a BMD -- somebody's been on the drug for five years. You measure their BMD at the hip. Whether you measure hip total BMD or hip femoral neck BMD, that BMD is related to fracture risk. Okay?

Now, Dr. Bauer described the change in BMD that occurs during an off-drug period. I didn't talk about that, actually, and maybe I shouldn't speak for Doug on that. But it's a different point, but also a very important point.

DR. CARSON: We'll have to stop here. We will have time to discuss it and FDA will pose, in

fact, questions to discuss. And if the panel does need more information during the discussion period to be able to answer those questions, we'll have time to direct them specifically to our presenters.

Thank you very much, sponsors, for your presentations.

[Applause.]

DR. CARSON: Now we'll break for lunch. We'll reconvene again in this room at 12:55 and start at 1:00 p.m. Please take any personal belongings that you need at lunch with you because the ballroom will be secured by FDA staff during the lunch break.

Panel remembers, please remember there should be no discussion of the meeting during lunch among yourselves or with any members of the audience. And the panel will be eating together. If we could just meet outside the doors, they'll show us where we're having lunch.

(Whereupon, at 12:11 p.m., a luncheon recess was taken.)

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

(12:59 p.m.)

Open Public Hearing

DR. CARSON: So let's begin. This is now the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

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

Likewise, FDA encourages you at the

beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Each speaker will have 3 minutes, except one speaker has been given additional time due to the donation of time by other speakers who have previously registered. Please speak only when recognized by the chair. Thank you all for your cooperation.

Let's begin. And please state your name before beginning. Yes?

MS. PEARSON: I happen to know I'm first, but I was waiting to see if you were going to call names. So my name is Cindy Pearson. I'm the executive director of the National Women's Health Network. We're an independent consumer advocacy organization, and by choice, we accept no financial support from any part of the industry, so we have no conflicts to declare.

We're here because we believe we, like everyone else who is speaking today, have a shared goal in supporting healthy aging and, in particular, to reduce hip fractures and to reduce the experience that undermines women's quality of life when they suffer severe vertebral fractures.

I'm sure we share the goal to have these benefits be available to women of color as well as white women. I know that's not a topic of discussion today, but I just want to bring that up because we who are familiar with these data sets know that most of the time, most of the studies are

mostly white women. So I just feel like that needs to continue to be said. And I'm sure we share the goal that as few women be hurt along the way towards helping as many women as possible to avoid hip fracture and severe vertebral fracture.

So the National Women's Health Network's position is based on reviewing all of the data which were posted online and listening very carefully this morning to presentations from the industry spokespeople, the invited guests, and the FDA. And we believe that the best balance of benefit to risk could be found if two things were to happen: one, if a common practice of discontinuing therapy somewhere in the three- to five-year range were adopted; and, two, if an unfortunately still too common practice of prescribing based solely on bone mineral density were stopped. Now, we believe both of these are important, and we're stressing the second one because, unfortunately, that happens still far too often.

The panel does have a chance to weigh in on

these issues today. The question posed by the FDA about what if any changes should be made to the label gives you, the advisors, a chance to recommend changes that we believe could lead to a preservation of the benefit and a reduction of women being hurt.

As you saw in your briefing materials, the FDA has estimated that 12 of every 100 women over age 55 has received a prescription for bisphosphonates at some time. Those women, for the most part, were symptom-free when they started. They are at risk of harm as well as benefit. You all have a chance to help women avoid that unnecessary harm without diminishing the benefit.

Thank you.

DR. CARSON: Thank you.

Speaker number 2?

DR. KLEBANOW: I'm Diana Klebanow, PhD. I'm an adjunct professor of political science at Long Island University.

I had a non-trauma femur fracture in April of 2002 after having taken bisphosphonates for

approximately five years. Five months later, I required another operation on my femur. I do not have ONJ.

I'd like to ask, to request, that the FDA issue a black box warning for atypical femur fractures and ONJ. I'm not engaged in any litigation over this matter. I'd like to present three items to you.

Item number one, a letter from Dr. John C. Stevenson of London published in the New England Journal of Medicine July 2011. A mention was made earlier about the Schilcher study; this is a rebuttal to it. I'd like to read parts of this letter.

Schilcher et al., May 5 issue), report the findings of a cohort analysis that examined the risk of atypical femoral fractures with bisphosphonate use. They found a statistically significant increase in such fractures, with an absolute risk of 5 per 10,000 patient-years, similar to that reported in other studies. They conclude that their results are reassuring for

1 patients taking bisphosphonates, since the
2 magnitude of the absolute risk is small. This
3 level of absolute risk appears identical to the
4 absolute risks reported for hormone-replacement
5 therapy, HRT, by the Women's Health Initiative
6 investigators, yet those investigators described
7 the risks of HRT as 'substantial ... This report
8 from the Women's Health Initiative led to
9 substantial reduction in the use of HRT, up to 50%
10 worldwide, but Schilcher et al. say that they find
11 the data on the risk of bisphosphonate use to be
12 reassuring.
13 Am I missing something?
14 Comment. Dr. Stevenson suggested the issue
15 regarding bisphosphonates is not how long they
16 should be taken but, as in the case of HRT, the
17 extent to which they should be taken at all.
18 Perhaps one day the FDA will need to consider this
19 issue as well.
20 I have another item, a position paper of the
21 American Association of Oral and Maxillofacial
22 Surgeons, an organization that was cited. They now

use the term "BRONJ," bisphosphonate-related ONJ. I've left copies of these items in the room, and I hope you'll feel free to pick them up and look at them.

Another item, a very interesting item from -- I still have time? -- from an orthopedic surgeon, Edward Yang, M.D., regional director, orthopedic surgery, Queens Health Network --

[Microphone off.]

DR. CARSON: Thank you. I'm afraid your three minutes are up.

Speaker number 3?

MS. BRYAN: Kerry Bryan, patient. I took Fosamax as prescribed from approximately 1997 to 2004, then Actonel from approximately 2006 until 2010. In between these bisphosphonate prescriptions, I was on a two-year Forteo regimen. I took my last dose of Actonel in April 2010 before receiving one annual infusion of Reclast the following month. I don't smoke. I've never taken steroids. I've never been diagnosed with cancer. And I'm 60 years old.

On the evening of March 2, 2011, I suddenly felt shooting pain in the area of my left hip. The pain gradually lessened, but I was sufficiently concerned to make an appointment to be seen at my doctor's office the next day. With scrip for pelvic X-rays in hand, I then went to the radiology department at Thomas Jefferson University Hospital nearby.

Upon leaving the hospital, I had walked less than two blocks, pushing a walker, as I had a metatarsal fracture at the time, when I felt the sudden sickening sensation of my left femur snapping when the walker hit a slight bump. I lost balance and toppled over onto my right side, which fortunately -- that's the other side -- fortunately was cushioned by the long down coat I was wearing. I fell because my femur broke. I did not break my femur because I fell.

I count myself lucky that this horrifically painful incident waiting to happen occurred so close to Jefferson, a superb medical facility. Within minutes, which seemed like an eternity of

agony at the time, I was whisked by ambulance to a trauma bay. I clearly remember someone in scrubs saying to me -- asking me if I've ever taken bisphosphonates. I replied yes.

The next day, I underwent emergency surgery to repair the transverse subtrochanteric fracture of my left femur. The expert orthopedic surgeon realigned my completely fractured bone before inserting an intramedullary rod extending from hip to knee. A few days later, I was discharged to a subacute facility for rehabilitation.

I began to explore information indicating that there is a relationship between prolonged use of bisphosphonates and occurrence of femur fractures not caused by external trauma. I learned that there are ever-growing numbers of cases remarkably similar to mine being reported. I also learned that many of these patients have experienced simultaneous or subsequent bilateral femur problems.

I shared this information with my surgeon during my first follow-up appointment. He promptly

ordered bilateral X-rays, took one glance, and immediately identified evidence of a stress fracture in my other femur, nearing the location of the left, as I underwent a second femur rodding on April 22, 2011.

I'll just conclude by -- I hope that the panel will know that these experiences have scarred many of us on many levels, and it is my profound hope that you will heed our stories and act sagaciously.

DR. CARSON: Thank you.

Speaker number 4?

MS. LAI: My name is Liyun Lai, and I'm 69 years old, a retired schoolteacher living in Canton, Ohio. At the recommendation of my OB/GYN doctors to prevent bone loss, I began taking bisphosphonates in 2001 for approximately seven years. During the end of the fifth year, I started to feel weakness in my legs when I walked or to carry a shopping bag.

A visit to orthopedic doctors in 2007, they suspect a knee problem and they suggest physical

therapy. However, it didn't improve the weakness in my legs. Later that year, I have broken metatarsal bones on my right foot without any reason.

In May 2008, I went to Dallas to visit my grandchildren. On May 31st, when I was in my granddaughter's room, I took a big step forward but my right leg collapsed. Fortunately, I was able to hold on the edge of the bed as I dropped to the ground. I had broken my right femur without any fall.

After is confirmed my femur was broken, I had surgery to insert a rod for the femur. The surgeon told me that there was a fracture also in my broken femur before it broke, and the fracture began from inside the bone.

Two months later, a bone scan X-ray on my other leg indicate it was a fracture broken approximately in the same location where I had a fracture on my right leg. The doctor said just surgery seems -- he felt it would break in time, even a walk. I decided to have surgery for the

second leg on September 16 the same year.

I am a strong, healthy, active person and enjoy outdoors and play with my grandchildren. After femur surgery, I have not been able to return activities I have enjoyed. My movements are strict and limited, and I have great deals of stress and anxiety because I'm unable to return to what I used to do.

I'm the great fear of the stress fracture in my body, not bone loss. For Fosamax, I'm asking of FDA to require black box warning on the drug indications, limit on the numbers of the years that medication can be given. Problem can occasion for the drug for osteoporosis, not for osteopenia.

Guidelines give clearer about the signs for a stress fracture and appropriate diagnosis and therapeutic intervention guidelines for the treatment for fracture with recommendations so the patient could closely watch due to slow healing and the patients not unique. Thank you.

[Microphone off.]

DR. CARSON: Speaker number 5?

DR. SHANE: My name is Elizabeth Shane, and I'm here to represent the American Society for Bone and Mineral Research. The ASBMR is a leading scientific research organization on bone health in the United States, and I'm an endocrinologist and professor of medicine at Columbia University in New York with many years of experience caring for patients with osteoporosis. I'm also a past president of ASBMR.

Because of our concerns about many of these things that these patients have been telling us about, the ASBMR convened task forces, and I had the opportunity to chair two of them, co-chair two of them, the osteonecrosis of the jaw and the atypical femur fracture task force.

Here are my disclosures. I have grant support from several pharmaceutical companies, but take no salary support from those grants.

The ASBMR task forces were international and multidisciplinary. They included experts in clinical bone disease, bone biology, epidemiology, and radiology. The ONJ task force included

dentists and oral surgeons, and the atypical femur fracture task force included orthopedic surgeons.

The task force members reviewed all published cases and a considerable amount of unpublished data on these two entities, and also interviewed the pharmaceutical companies that market drugs for osteoporosis.

The key findings of the task forces -- of the ONJ task force, updated with some recent findings, is that the risk of ONJ with bisphosphonate therapy for osteoporosis and Paget's disease is low, between 1 in 10,000 and less than 1 in 100,000 patient treatment years. The risk of ONJ with high dose bisphosphonates for cancer is higher, affects from 1 to 10 percent of patients, and increases with duration of treatment.

The key findings of the atypical femur fracture task force are that studies that included radiograph review, in our opinion, clearly showed an increased relative risk of atypical femur fractures with bisphosphonate therapy.

That being said, the absolute risk of

atypical femur fractures is low, as they account for less than 1 percent of all hip and femur fractures. We estimated the risk at from 1 to 5 per 10,000 bisphosphonate-treated patients. The risk appears to increase with duration more than five years. The risk of typical hip fractures is higher and is decreased by bisphosphonate therapy.

In summary, bisphosphonates are important drugs that lower the risk of common osteoporotic fractures. The relative risk of both ONJ and atypical femur fractures are increased in patients on bisphosphonate therapy, and probably also with long-term use. Bisphosphonates have not been shown to be causal for either. The absolute risks of ONJ and atypical femur fractures are very low. Bisphosphonates prevent many more fractures than they may cause.

We recommend that bisphosphonates be reserved for patients who are high risk of fracture, certain cancers, and Paget's disease, and we recommend more research on benefits and risks of long-term bisphosphonate therapy before limiting

use to five years.

Thank you.

DR. CARSON: Thank you.

Speaker number 6?

MS. LEVIN: My name is Betsy Levin. I'm here as a patient. I took Fosamax for seven years, starting at age 67, after stopping HRT and with a DEXA scan showing a slight drop in bone density. I had none of the indicators for osteoporosis. I was in good health, an active runner and a hiker. My internist indicated Fosamax would prevent possible osteoporosis, but had no serious side effects and was to be taken for the rest of my life.

July 2010, after having hiked in Turkey in May, after three weeks of increasing pain in my left thigh, which my doctor attributed to a muscle pull, I experienced a complete fracture of my left femur as I took a step forward out of my kitchen. I fell to the floor as a result of the fracture, where I lay in excruciating pain, screaming for nearly an hour, until I could finally reach my cell phone to call 911. I was taken to the hospital and

had a titanium rod inserted. Until my fracture, my internist knew nothing of this possible side effect of bisphosphonates.

After nearly three weeks in the hospital and its rehab center, I was released to home health care. But because of a blood clot that occurred during surgery, I returned to the hospital a week later to have a filter implanted in my inferior vena cava. And it was removed in another hospital procedure seven months later.

On the recommendation of both my internist and my orthopedic surgeon, I consulted an endocrinologist, who determined that I had never had osteoporosis and possibly never even had osteopenia. I was just old.

In November 2010, after some pain in my right thigh, I had an X-ray that showed microfractures in almost the same place as the left femur, and I again had surgery to insert a titanium rod, followed by several weeks again in the hospital and its rehab center. I am still undergoing physical therapy for both legs.

Fosamax is said to have a half-life of 10 years, although I guess research hasn't really made that clear. But many others with bisphosphonate and femur fractures have also had metatarsal fractures. I still worry with every step that I take.

Based on my experience, I urge the FDA to, one, include a black box warning for all bisphosphonate drugs; recommend that bisphosphonates not be prescribed for osteopenia at all, and in cases of osteoporosis not be taken for more than five years; provide guidelines to medical personnel and others that include the signs for a femur stress fracture; and require hospitals to keep a registry of patients presenting a nontraumatic femur fracture, thus providing the FDA with more accurate information on the number of bisphosphonate-caused femur fractures.

Thank you very much.

DR. CARSON: Thank you.

Presenter number 7?

MS. COOK: Good afternoon. My name is

Andrea Cook. I'm here at my own expense on behalf of my father, Milton Jessup (ph), and my family. This is a picture of my father. He is not able to be here today because the drug Reclast claimed his life 54 days after his first IV infusion.

I've been given three minutes to talk about days of suffering, and months of research, and numerous conversations I've had with other victims of this drug. This is not nearly enough time, but it's what I've been given.

What I have to say as quickly as possible is this. Before Reclast, my father lived independently. He played golf twice a week. He helped look after his grandchildren. He traveled extensively. He loved this country, and he believed in the good in people.

Like so many other victims of this drug, my father believed and trusted that his doctor was looking out for his best interest. This was a mistake, a mistake that we can't take back.

My father followed all procedures and protocols for this drug. He had a complete blood

workup before his infusion. All the blood work came back normal. His kidney function, his B-U-N, or BUN, was 22 before he took Reclast. Less than three weeks later, it was 41.

Three days post-Reclast, his problems started. When Reclast had finished with my father, his list of symptoms and health problems included muscle spasms, severe bone pain, atrial fibrillation, renal failure, fluid around his heart and in his lungs, respiratory problems, and this is the short list. Before Reclast, my father was taking one prescription medication. After Reclast, he was taking more than 10. Everyone that knew my father had no doubt that Reclast was responsible for his death. This drug devastated my father and our family.

I humbly and respectfully ask that you open your eyes to what was happening. Are these drugs truly helpful? I have yet to find any credible evidence, certainly not worth the risk. Reclast is especially dangerous, as it can't be reversed and there is no antidote. This is a game of Russian

roulette played with human lives.

I am one of many people that have lost a loved one. You need only go as far as your computer and Google Reclast and you will hear from people who have forever been altered because of this drug. They couldn't make the trip because they were too ill.

I am not here to cast blame or point fingers. I'm not looking for a scapegoat. I'm here for truth; truth, not excuses, and certainly not to be appeased. I pray that each one of you open your hearts and ears to what you are hearing. We are the evidence you need. These drugs are a mistake.

These warnings are not enough. Please have the courage and do the right thing. These drugs need to be pulled from the market, period. There's a profound saying that states, "You cannot serve two masters." Please choose not to serve money. Money is temporary; people matter.

Thank you.

DR. CARSON: Thank you.

Speaker number 8?

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman. I'm president of the National Research Center for Women and Families and the Cancer Prevention and Treatment Fund, and I have no conflicts of interest.

I'm speaking from my perspective as a former faculty member at Vassar and Yale, a research director at Harvard, and I'm also currently at the University of Pennsylvania Center for Bioethics.

So my perspective is as someone trained in epidemiology at Yale. And, as such, I urge you to look at the data and focus on the meaningful data. You've heard a lot of different interpretations of the data already today.

We need to focus on the real benefits, and that means helping patients live happier and healthier lives. Bone density doesn't really give us that information. So we really do need to look at fractures in terms of benefits as well as the kinds of risks that we've heard about in the last few minutes.

There's no proof in the data -- and I've looked at this very carefully. There is no proof of benefits for these drugs when taken for more than five years in terms of meaningful benefits. There's also a clear pattern of increased risks. The longer these products have been on the market, the more risks we know about. And you've heard the human side of that in the last few minutes.

But even just looking at the data, there's already some evidence. And we can only assume that if more studies are done, we'll know more. We don't know exactly what we'll find out, but we do need better research, long-term research. So how are we going to get that information?

I also want to specifically say that of course cancer usually takes about 15 years to develop, so it's going to be quite a while before we know whether these drugs do increase the risk of cancer. It does look like that's possible, but we'll need better data to find out.

So what we need are better long-term studies. And in the meantime, we need a label that

protects patients. And so that label should, I believe -- and I urge you to recommend that the label make it clear that these products be taken for up to three years, and that there's no benefits if taken more than five years, and that there is some evidence of risks after three years.

When companies are asked to do postmarket studies, they're just more likely to do better postmarket studies if they have an incentive to finish those studies and do them carefully. And by having a label that restricts usage, that gives the companies incentive.

If they can prove that these products really have added benefits if taken for more than five years, and that those benefits outweigh the risks, then that label can change. But until then, I urge you to be cautious in protecting patients and basing your recommendations on the data that are available.

Thank you.

DR. CARSON: Thank you.

Speaker number 9?

MS. IEHL: Hi. My name is Jerri Iehl, and I'm from Waterloo, Iowa. I came to you today, paying my own way, because I felt it was important to let you know of the devastating effects of Reclast and how it's affected my life.

I had a bone scan in early May of 2010 with the resultant T-score of minus 3.8 at the femoral head. My doctor recommended taking Reclast. I had that Reclast on May 27th of 2010. The intake nurse at Covenant Hospital instructed me to drink plenty of fluids and stated that I might have some flu-like symptoms for a day or two; but other than that, she said I should be fine.

The next day, I felt like a Mack truck had run over me, and I was running a fever, and I had bone pain like I had never known. Two weeks later I had a lump appear on my wrist, which was hard and painful to the touch. When I saw my doctor, I asked him about it, and he said it was a bone spur.

To date, I have between 80 and 90 bone spurs all over my body, all confirmed by either X-ray, MRI, or CAT scan, with some on my hands, gnarling

my fingers; some on my feet, making it difficult to walk; my back, making it difficult to sit or stand for any length of time; my shoulders, esophagus, ribs, and the most dangerous ones are in my lungs.

I also have had issues with my teeth as well. It was necessary to have two teeth pulled as a result of an infection in them. I ended up with exposed bone in the back of my jaw. The University of Iowa's dental department diagnosed me as having the beginning stages of osteonecrosis of the jaw. They said that I cannot have any of my other teeth removed or I would run the risk of having no teeth at all. They will try and fit me with dentures, but at this point it is uncertain whether they will be successful at all.

Since being infused with that one dose of Reclast, I've had several other medical events, for which I brought documented proof with me today, that have all been attributed to that one infusion of Reclast. Some of them are as follows:

Atrial fibrillation, a month and a half post Reclast infusion, which was unsuccessfully

corrected by cardiac ablation;

Gastritis and gastroparesis, which was treated by inserting a feeding tube after my weight dropped to a dangerously low level of 89 pounds and my blood pressure dipped to 46/20;

Five episodes of pneumonia and one of the flu within a year's time frame, which I had to be hospitalized for, that led to a diagnosis of cytoglucopenia secondary to that single infusion of Reclast;

Surgical excision of a bone spur on my left wrist due to a nerve blockage, documented by a nerve conduction study;

Filing of an adverse reaction to Reclast report filed by my physician to the FDA as a consequence to all the above.

Reclast, as you can see, has been a nightmare for me. I have had multiple adverse events which have had a harmful effect on my body resulting from that one infusion of Reclast.

Thank you for your time. Please consider my experiences with Reclast as you consider the future

1 of bisphosphonates. Thank you.
2 DR. CARSON: Thank you.
3 Speaker number 10?
4 DR. ALMASHAT: Hi. My name is Dr. Sammy
5 Almashat from Public Citizens Health Research
6 Group. I'm testifying today on behalf of myself
7 and our group's director, Dr. Sidney Wolfe. We
8 have no financial conflicts of interest.
9 Given the serious risks discussed in today's
10 meeting, it is critical that a rigorous
11 risk/benefit profile be developed for all
12 bisphosphonate users to determine those women who
13 will actually benefit clinically from therapy.
14 I'll discuss today two patient populations in whom
15 the drugs have not been shown to decrease fracture
16 risk, the critical endpoint, one being
17 postmenopausal women with osteopenia, that's
18 already been discussed; and, two, all
19 postmenopausal patients remaining on the drugs
20 beyond five years.
21 Osteopenia is a condition that was heavily
22 promoted to expand the market for Fosamax to

1 millions of otherwise healthy women. Yet all
2 randomized trials of bisphosphonates in women
3 without osteoporosis have only shown an improvement
4 in a surrogate marker, BMD, and not fracture risk,
5 the only relevant clinical endpoint here.
6 The largest trial to evaluate this endpoint,
7 FIT, failed to show any clinical fracture benefit
8 of Fosamax for osteopenic patients after four years
9 of use. Furthermore, bisphosphonates are currently
10 approved to treat not only all osteopenic patients,
11 regardless of fracture risk, but virtually all
12 postmenopausal women. According to the Fosamax
13 label, treatment can be considered in women with a
14 "thin body build" and those of "Caucasian or Asian
15 race as risk factors," thus including in its
16 indicated population almost all postmenopausal
17 American women. To our knowledge, this is an
18 unprecedented scope of use.
19 By contrast, the National Osteoporosis
20 Foundation, as discussed today, recommends
21 bisphosphonate use only in osteopenic patients at
22 high risk for hip or other fractures at 10 years,

using the FRAX algorithm.

The other patient population are those who take bisphosphonates for greater than five years. The landmark FLEX study also showed no clinical benefit of Fosamax in almost all postmenopausal patients beyond five years, even in high-risk women with osteoporosis and a history of vertebral fracture.

This lack of benefit on fracture incidence extends to all other oral bisphosphonates, as found in the FDA's pooled analysis. The FDA staff concluded correctly that, "These results suggest no significant advantage of continuing drug therapy beyond five years." We should not allow the sponsors' assertions today of continued benefit based primarily on PK or BMD data to cloud the picture. What matters are prespecified clinically significant endpoints.

Prolonged use greater than five years also exposes patients to increased risk, as the rates of both atypical femur fractures and osteonecrosis of the jaw have been shown to increase three- to

1 fourfold beyond this point. Thus, the use of
2 bisphosphonates in these two populations needlessly
3 exposes women to serious risks with no evidence of
4 clinical benefit. This risk/benefit profile is
5 completely unacceptable. Therefore, we urge the
6 committee to recommend the following to the FDA:
7 One, long-term use of bisphosphonates for
8 the prevention of osteoporotic fractures must be
9 limited to five years, with off-label use only
10 considered on an individual basis; and, two, the
11 indication for bisphosphonate treatment for
12 osteopenic women must be removed unless the patient
13 is at a high 10-year risk for clinical fractures,
14 as determined by the FRAX algorithm.
15 Thank you.
16 DR. CARSON: Thank you.
17 Speaker number 11?
18 DR. BUNNING: I'm Robert Bunning, and I'm
19 the medical director of National Rehabilitation
20 Hospital, the director of the orthopedic program.
21 I work as a full-time physician at NRH for the last
22 25 years as a practicing clinician/administrator.

I've also provided limited medical and legal consultations, and earned fewer than $2,000 over the past two years.

One of my jobs at NRH is to present interesting cases to the residents. In 2006, I saw my first unusual case of a mid-femoral fracture with no trauma. And later that year I saw a second case, and then two more cases. These cases were unusual enough that we published them, one as an abstract and then four as a case series. Details are available in these publications. Since then, I have treated five more patients. And due to time limitations, I'll present a brief sketch of three of these patients.

The first patient was an 82-year-old woman who came to us in 2010 following surgical fixation of a nonunion of her right femur. She started Fosamax in 2001. In 2008, while walking in her kitchen, she collapsed to the floor. She had a mid-femoral fracture. It did not heal. She remained on her bisphosphonate. Later she stopped it, and this was the fixation she presented to our

hospital with.

During the time with us, we did an X-ray of her other side to assess for a stress fracture. On the left panel is that X-ray that was obtained. It doesn't show up that well, but it showed a clear indication of a stress fracture. Over two months, she had progressive pain, requiring rodding for the femur shown on the right.

The second patient was a 77-year-old woman who came following surgical fixation of a left femur fracture. She was walking in her home office when she tripped, heard a crack, and fell to the floor. This is her plain film. This is her MRI. She had been diagnosed with non-Hodgkin's lymphoma. She received Zometa infusions from 2006 to 2010 as a treatment.

In 2009, while still on Zometa, she had a stress fracture documented; however, she continued on Zometa. In 2011, this progressed to the completed fracture, which I have just shown you.

Patient three was an 80-year-old woman. Walking to her car, she felt her leg give out. Her

son caught her; she never hit the ground. She fractured her left mid-femur. She came for rehabilitation. This is the fixation. That fracture healed well. She'd been on a bisphosphonate 15 years.

During the time with us, we discussed whether or not we should rod her opposite leg. She had no symptoms at that time. We discussed the risk and benefit with her and her son. They decided not to have preemptive surgery.

She was discharged from rehabilitation. However, two weeks later I got a call from her son stating that while standing in her bedroom, she had felt her right leg give out, where she sustained a right femoral reverse oblique fracture in the subtrochanteric region. That was successfully treated.

My experience suggests long-term bisphosphonate therapy may cause low impact horizontally situated mid-femur or subtrochanteric fractures. The frequent bilateral distribution and close temporal association, combined with the low

impact history, suggest a mechanism of metabolically induced bone fragility.

Thank you.

DR. CARSON: Thank you.

Speaker number 12 will have six minutes.

DR. SCHNEIDER: One morning 10 years ago, as I was riding New York City subway, the train jolted and I shifted my weight to my right leg. I heard and I felt my femur crack, and I fell to the floor.

I'd had pain in that thigh for about three months. I'd had it X-rayed, and I was told it was fine. At that time, I'd been on Fosamax for osteopenia for several years starting in 1995, not for osteoporosis. In fact, I was a speaker for Merck at that time on Fosamax because I'd had such great results with my bone density improving, and I was told nothing at that time about the possibility of any type of over-suppression of bone turnover. Here's what my femur looked like at that time.

So in the emergency room, another doctor at the orthopedic hospital to which I was taken found it hard to believe that I had not had a high-speed

auto accident, nor did I have metastatic cancer anywhere. I had a rod inserted in the leg and received two units of blood from blood loss, but that wasn't the end.

The bone didn't unite for many months. And month after month, my X-ray looked exactly the same. Finally, after eight months, I had a second surgery to replace the rod with a larger one, which eventually healed. Then a year or two later, I had a fracture of a metatarsal bone in my foot as well, and that, too, had delayed healing. My urinary NTx remained quite suppressed for several years after I stopped the Fosamax.

A few years later, I wrote a paper about my bizarre fracture, which was published in a medical journal and also was available online. After a while, I began getting emails from other people who had come across my article, or another one I subsequently wrote in another medical journal. And these people had remarkably similar stories to mine after years of taking Fosamax. This is a picture of the femur of one of them, Phyllis.

I began an email support group, which turned into a grassroots movement. We now have about 120 members. We found ourselves educating our doctors, many of whom still don't understand what is different about atypical femur fractures, and don't even realize that there have been recent changes in the patient package inserts of bisphosphonates relating to the AFFs.

Recently I collected data from the group members, and along with one of the computer-savvy group members, Christina Sou (ph), who knows statistics quite well, we analyzed the data and I'd like to present some of it. I don't have a lot of time, so I'm only going to kind of gloss over the main findings. But there was this handout that I had given you.

So why are my results relevant? Probably the best epidemiologic study on the risks of atypical femur fractures is a Canadian study published last year by Park-Wyllie in JAMA. She found that women who took bisphosphonates for at least five years had a risk of about 1 to 500 of

sustaining an AFF, according to Dr. Joseph Lane, whose conclusions were published about three weeks ago in the Journal of Bone and Joint Surgery on August 17th.

In 2008, we heard this morning, 5.1 million people were prescribed a bisphosphonate. According to Dr. Kuyateh this morning, about 2 percent of them took it for over five years, at least five years, and that's about 10,000 people. At a risk of 1 in 500, that's 200 AFFs, which is not so rare.

Although most orthopedic surgeons are seeing such cases, the published clinical articles are mostly 15 to 20 cases. The present study is much larger, 111 people, large enough to gather some statistical meaningful information about the features of AFF.

So I'm going to go through this quite quickly. We had 108 women and 3 men, 85 percent of them with at least one completed femur fracture. The other had a stress fracture, an incomplete fracture. The age at the first fracture was only 65. These are not very old people. Thirty percent

also had a metatarsal fracture. I think this is a totally unrecognized aspect of the susceptibility to bisphosphonates.

Thirty-five percent had involvement of both femurs, like some of the cases that you just heard. I mean, this is a very high risk. In the course of the study, I asked the people for some documentation of the type of fracture they had, and 51 percent sent X-rays and/or reports to confirm that indeed that's what they had.

Most of them were initially begun on Fosamax, and 70 percent were initially begun on a bisphosphonate for osteopenia. And that is an important point here, that most of us were not even getting this for osteoporosis.

The dose for osteopenia, 65 percent were begun on the dose that's not FDA-approved, the 70 milligrams per week. Fifty-three percent used only Fosamax, three only Actonel, and one only zoledronic acid. And the remainder took Fosamax plus one or two other bisphosphonates. Before their first fracture, 9.3 years was how long they

took it, which was considerably longer than the five years.

As far as pain, most of them had preceding thigh pain, which actually is probably an indication of an undiagnosed stress fracture. Only a few of them did have a diagnosis. Most of them had sought treatment for persistent thigh pain or leg pain, and they had multiple unsuccessful treatments, quite expensive, quite invasive in some cases. You can look at this later. These people did not have a stress fracture considered as their diagnosis, so they had all of these unnecessary procedures. And 35 percent of them had fractured both femurs, and 22 of those had a contralateral stress fracture, all of which were prophylactically rodded, a good thing. Ten of them had a contralateral completed fracture.

The final thing I want to say is that almost 40 percent of both groups completed in stress fractures had a delay in healing, with a mean time of healing of 15 months. And I forgot to say that of those who had two complete fractures, the mean –

–

[Microphone off.]

DR. CARSON: Before you leave, Doctor, would you just read your name into the record, please?

DR. SCHNEIDER: I'm sorry. Jennifer Schneider.

DR. CARSON: Thank you.

Speaker number 13?

MS. MATTHEWS: My name is Jean Mathews. I'm from Rome, Georgia.

On Mother's Day Sunday of 2009, I went outside early in the morning to get my newspaper. As I came back in my house, I took one step, and my leg broke in half. This is after three to four months of thigh pain that I experienced. I had had physical therapy. I had had X-rays. I had visited an orthopedic surgeon. I had changed office chairs.

I have been a participant in Dr. Schneider's online support group, and I am going to go over the summary findings of the study because her time was so limited. Let me go very quickly through that.

Almost everyone in the group had taken a bisphosphonate for five years or more, and most were prescribed for osteopenia, and that includes me. I didn't think I was even old, but I was at risk; my mother had had that.

Usually everyone had some kind of leg pain, although there were a few who had not. And most of us did undergo those expensive and unsuccessful attempts to find out what was wrong with us. Of those who had stress or completed fractures, as Jennifer mentioned, 35 percent in the group had contralateral femur fractures, either stress or completed fractures.

Obviously, those who had the contralateral fracture, the problems persisted for about two years, so up to two years before they may have had another one. The stress fractures were at a high rate for a completed fracture. And delayed healing is something many of us have experienced in the stress fractures and also in those with completed fractures. I myself have had three surgical procedures, including a re-rodding of my femur and

a bone graft at the site almost two years after my initial surgery.

In addition, as she mentioned, a number of people, more than 30 percent in the group, have experienced other types of fractures, in particular the metatarsals. I have had four metatarsal fractures, with no trauma, just walking across the floor.

So this is something we will now begin to urge women and men to start to report to the FDA. We have reported our stress fractures and our completed fractures. We have not been reporting the metatarsal fractures, and that's something we would urge you to take a look at.

Thank you.

DR. CARSON: Thank you.

Speaker number 14?

MS. WRIGHT: My name is Karen Wright, and I'm going to complete the rest of Dr. Schneider's presentation.

I was diagnosed with osteoporosis, and I took Fosamax for eight years. Two years ago, at

the age of 62, my femur fractured as I was walking up one step. I was hospitalized for two weeks and had physical therapy for six months. Prior to this fracture, I had thigh pain for nine months, and I also had two fractured metatarsals and a fractured fibula.

Four months ago, because of continuing pain from the fracture two years ago, I had that rod removed and a shorter rod inserted. Again, I was hospitalized for two weeks, and I'm still going to physical therapy.

I thought I was being proactive by taking Fosamax, ensuring that I could continue an active lifestyle, working, traveling, and enjoying my family, just as is advertised. It was not to be. And because of the condition of my bones caused by Fosamax that will be with me for years to come, I no longer work outside my home, am very cautious about every activity, hesitate to travel far from medical care, and constantly worry about another fracture. It's a completely different lifestyle than I imagined.

We would like to request that a black box warning be added to all packaging. This will bring the appropriate attention to the issues that need to be considered before bisphosphonates are prescribed. Direct communication with the medical community is essential, and only the FDA has the resources to do this.

The black box warning should include information about stress and complete fractures, that they are often bilateral, and that the contralateral femur should be examined. Upon diagnosis of either a stress or complete fracture, bisphosphonates should be discontinued.

Patients often present to their physicians with thigh pain. A stress fracture should be part of the differential diagnosis and the appropriate imaging studies performed. General practitioners, orthopedists, neurologists, physical therapists, and even those who work at fitness centers should all be aware of the connection between bisphosphonate and fractures.

Stress fractures are at a high risk of

1 becoming a complete fracture, and should be
2 prophylactically rodded. And these fractures often
3 result in delayed healing, requiring additional
4 medical intervention.
5 Patients remain at high risk for fractures
6 for many years after five years of treatment, and a
7 diagnosis of osteopenia should not be the only
8 factor considered for whether or not
9 bisphosphonates should be prescribed. Without the
10 black box warning, all the data that you've heard
11 today is not going to be presented to the general
12 public, and the black box warning would ensure that
13 the information is distributed.
14 Thank you.
15 DR. CARSON: Thank you.
16 Speaker number 15. And for the remaining
17 speakers, let me remind you to please read your
18 name into the record before you begin.
19 DR. TOSI: Hello. Good afternoon. My name
20 is Laura Tosi. I'm an orthopedic surgeon from
21 Washington, D.C. I'm speaking today on behalf of
22 the American Academy of Orthopedic Surgeons.

My conflicts are listed. I have never personally received money for my advocacy; to the dismay of my husband, I serve the bone health community primarily in a volunteer capacity.

Now, I want to thank the FDA for convening this meeting today, and it's a sad fact that most of us will never grow up to look like Sophia Loren. But many of us in this room, particularly the women, will live to be 100 years old. That news is a mixed blessing, however. Unfortunately, 1 in 2 women and 1 in 4 men over 50 will experience at least one fracture in their senior years.

Now, orthopedic surgeons are very proud of what we can do to repair most injuries. But harsh facts remain. Fractures kill. Fractures, particularly hip fractures, severely increase mortality rates, and, sadly, fracture survivors, like the older women in this photo, can experience and expect a significant loss in their independence.

Now, the orthopedic community has been most excited by the data demonstrating not only marked

reduced fracture rates in patients treated with bisphosphonates, but reduced mortality as well. In response, our professional organizations are moving forward on several quality initiatives aimed at improving fracture care. I'd like to outline two of them.

Own the Bone. Now, that doesn't mean orthopods own it. It means we're asking orthopods to take responsibility for the bone. Own the Bone is a national post-fracture quality initiative intended to ensure that fracture patients are provided evidence-based care aimed at preventing repeat injuries.

In addition, the American Academy of Orthopedic Surgeons is in the process of developing an evidence-based clinical practice guideline that will explore all aspects of hip fracture care. We believe this is an essential step to reducing the disappointing morbidity and mortality rates faced by hip fracture patients.

I hope you've enjoyed some of the public service announcements included in this

presentation. The AAOS has sought to increase the public's awareness of the importance of bone health across the age span for over a decade.

Now, if our orthopedic surgeons are going to take good care of patients, we need answers to the many questions listed and discussed today. We need to give them the best possible data to improve patient care. Our seniors deserve the very best, and if our doctors know more, we can do a better job.

We appreciate the efforts of the scientific community and the FDA for holding this conference today. We are honored --

[Microphone off.]

DR. CARSON: Thank you very much.

Speaker number 16?

MS. UNANSKI: My name is Carol Unanski, and I'm a recently retired teacher from the Holmdel School District in Holmdel, New Jersey. My history with Fosamax started in August of 2000. Since I was 55 years old, Dr. Margaret Lambert-Woolley, my gynecologist, felt it was time for a bone mineral

density test. The DEXA report indicated osteoporosis of the hips, and a recommendation was made by Dr. Lambert-Woolley to begin a course of treatment that involved taking 10 milligrams of Fosamax daily. When a weekly pill of 70 milligrams plus D became available, I then made a transition to the weekly dose.

I continued to have annual bone density tests for the next nine years. On March 17, 2009, my ninth BMD test was completed and evaluated by Dr. Beth M. Deutch, proprietor of HerSpace Breast Imaging Associates in West Long Branch, New Jersey. There was insignificant change in the bone mineral density of the femoral necks. At this particular visit, Dr. Deutch indicated I would be approaching nine years of being on Fosamax, and her medical opinion was I needed to take a holiday from the drug.

On March 26, 2009, Dr. Lambert-Woolley forwarded me a letter indicating she had received the results of the recent BMD test, and concurred I should stop the Fosamax, which I did in April. In

summary, my usage of Fosamax spanned from August of 2000 until April of 2009.

On May 8, 2009, I proceeded to push a small student desk, which was located under my classroom dry board, when I realized I was losing my balance. I reached up to the dry board with my left hand and was able to balance myself without falling. I looked down and saw my right leg was totally mangled. The leg was in the air, and my right foot had rotated 180 degrees. I was looking at my right foot, which was completely backwards. The femur bone had broken in the presence of my 26 fourth-graders.

The break occurred on May 8th, and on May 9th, emergency surgery was performed to repair the femur fracture. I remained in the hospital for 14 days, where I underwent acute rehabilitation. Rehabilitation continued as an outpatient for seven months.

During the course of physical therapy, Dr. Steven Friedel, the orthopedic surgeon who repaired the fracture, determined a nonunion

healing had developed. A second surgery was performed on September 17, 2009 to encourage the proper healing of the femur. The static screw was replaced with a distal screw above the kneecap, and bone marrow was aspirated with a harvest system of the right proximal femur.

At present time, I am taking nothing for the treatment of osteoporosis, as Dr. Joseph Lane, a bone cancer and metabolic bone specialist and chief of osteoporosis at Hospital for Special Surgery in New York City, tries to make a clinical decision as to what is the proper course of treatment after being on a daily shot of Forteo for the past two years.

Thank you so much for your time.

DR. CARSON: Thank you.

Speaker number 17?

MS. LANTER: Good afternoon. My name is Orrel Judith Lanter. I'm here from California to tell you my story.

My passion in life is hiking and biking. I have always been extremely active and athletic. I

take vitamins and eat a mostly organic vegetarian diet, and had been on Fosamax and its generic equivalent for nine years.

I had heard of problems with necrosis of the jaw with use of this drug, and had expressed concern to my primary care doc. But there was nothing in the literature that comes with the pills that said anything about the potential for atypical femur fractures, which would have helped us make an informed decision on risks versus benefits.

For years, I have walked a minimum of three miles every day or biked 25 a week. This year, in order to keep active, I had my left knee replaced. My knee ortho said the bones look good. The month prior to knee surgery, I had seen an article that said a number of individuals who had been on Fosamax were experiencing atypical femur fractures. Alarmed, I told my primary care doc I was taking myself off the drug.

After knee surgery, I was released from hospital and rehab and sent home to do exercises. I was healing admirably. Then I began to notice

pain in my right thigh area, which continued to worsen for the next few weeks. I got X-rays.

May 24th, my ortho said the knee X-rays looked good, and the hip and femur film showed only minor arthritic changes. On May 25th, I went to physical therapy and told my therapist the knee seemed to be doing well, but I was having a lot of pain in the right thigh area and could only walk using a cane. May 27th was my second physical therapy of the week.

May 28th I went to Costco, turned to put a piece of paper in the trash, and felt something go snap in my right thigh. My right foot flopped out to the right, and my leg became a noodle. The pain was excruciating.

The ambulance took me to the ER. They X-rayed my leg. The ER doc said it was an atypical femur fracture. I said I bet it's due to the Fosamax I was taking for the past nine years, as it was exactly what had been described in the articles I had recently read. He agreed.

The surgeon put a rod in my femur going from

knee to hip, held by long screws that I constantly feel through my skin. It was impossible for two months to sleep on that side because of the pain. My knee therapy, which was so crucial in that first month of healing to be able to get the most flexibility and future mobility, stopped as the therapy concentrated on the fractured femur.

It may take years for the bisphosphonate to leave my system. I live each day with the unnerving potential of a second fracture to the other femur. I was a healthy, happy, very active outdoorswoman in the prime of my life, now left crippled by this awful drug. Believe me, there is no benefit to having a spontaneous femur fracture. I never would have taken the drug. I think it should be black boxed.

Thank you.

DR. CARSON: Thank you.

Speaker number 18?

DR. RECKER: Good afternoon. My name is Dr. Robert R. Recker. I'm director of the Osteoporosis Research Center at Creighton

University in Omaha, Nebraska, and I'm here as president of the National Osteoporosis Foundation, which is the leading consumer and community-focused health organization dedicated to the prevention of osteoporosis and fractures.

The NOF accepts support from a wide range of diversified sources, including individuals, foundations, government sources, and corporations. And I have been a consultant and received research support from the industry personally through my institution. Thank you for providing this forum.

Osteoporosis and low bone density affect about 44 million Americans, and without treatment, 1 in 2 women and 1 in 4 men will break a bone after age 50 because of osteoporosis. These fractures cause death and disability, and there are about 350,000 hip fractures annually in the U.S. About 20 to 25 percent of the people with them die in the year following the fracture, and about 50 percent of survivors require long-term assistance for activities of daily living. Yet many people do not know their risk for the disease, even after they

fracture.

Bisphosphonate treatment can reduce the risk of fractures in people with osteoporosis by 40 to 50 percent, as you've seen. In addition, greater compliance with bisphosphonate treatment results in greater reduction in fracture rates, and thus bisphosphonates often are prescribed for the prevention and treatment of osteoporosis.

Two safety concerns have emerged with bisphosphonates and have occasioned this conference, namely, osteonecrosis of the jaw and atypical fractures. However, less than 1 percent of the osteoporosis patients taking oral bisphosphonates suffer ONJ, and, of course, good dental health should be assured before prescribing them; and this risk should be contrasted with the risk of fracture in patients with osteoporosis. Similar things are present for the atypical hip fracture.

But it should be pointed out that both ONJ and atypical fractures also occur rarely in patients who have never been treated with an

osteoporosis drug. Patients who have fractured or who are at high risk of fracture should be treated with effective medications, and this includes bisphosphonates. They should be educated to know the warning signs of ONJ and atypical fractures. They should be assessed regularly to determine whether continuation of therapy is appropriate.

The NOF strongly believes that for most patients, bisphosphonates are an important weapon against osteoporosis and associated fractures, and their benefits outweigh the risks. A potential for rare adverse events of ONJ and atypical fracture should be weighed against the benefit, patient by patient, and if patients have side effects, unusual symptoms, or questions, they should be encouraged to talk to their healthcare providers. And I might mention, the NOF and sister organizations are considering sponsoring a consensus conference to help clinicians with the clinical dilemma discussed at this conference.

Thank you very much.

DR. CARSON: Thank you. Thanks to all of

the public hearing speakers. And also, we have received a number of letters from patients that I'm sure the panel has read. And I know it's very difficult sometimes to relive moments of pain, and appreciate all of you taking the time to tell us about that.

So the open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience unless specifically requested by the panel.

We will now proceed with a summary presentation from the FDA. I would like to remind public observers again at this meeting that while this meeting is open for public observation, public attendees may not participate except, again, at the specific request of the panel.

So Dr. Theresa Kehoe will once again come up and summarize the meeting.

FDA Presentation - Theresa Kehoe

DR. KEHOE: I'm not sure what happened to the slide that -- okay. Well, we'll get started anyway.

So you've heard a great deal of information that's been presented today from FDA, the invited speakers, our industry sponsors, and the public, including professional societies, academic experts, practicing physicians, and individual patients. I am now tasked with trying to pull it all together.

We have heard that bisphosphonates are highly efficacious in reducing the risk for fracture, and they are widely prescribed for the prevention and/or treatment of osteoporosis, with upwards of 4 to 5 million patients over the age of 55 filling an outpatient prescription annually. Although bisphosphonates are widely prescribed, drug use data suggests that a minority of patients continue therapy beyond three years.

Recent events have raised questions regarding the safety of bisphosphonates when used for years and used widely, most notably, atypical subtrochanteric fractures, osteonecrosis of the jaw, and the question of esophageal cancer with oral bisphosphonates. We recognize that the adverse event reporting system data are generally

not helpful in assessing for these rare safety events.

For typical subtrochanteric and femoral diaphyseal fractures, there may be an association between bisphosphonate use and these fractures. However, the relationship between atypical fracture and the duration of bisphosphonate use remains unclear.

For osteonecrosis of the jaw, based on the limited numbers of cases in the PROBE study, it appears that the prevalence of osteonecrosis of the jaw may increase with increased duration of exposure to oral bisphosphonates, with the highest prevalence at four or more years of use.

For concerns regarding esophageal cancer, available evidence is inconclusive regarding an association between esophageal cancer and oral bisphosphonate use.

From the efficacy perspective, placebo-controlled clinical trial data out to a minimum of three and a maximum of five years is available. Additional clinical trial data on bisphosphonate

extended use is available out to 10 years, with various trial designs, including randomized withdrawal trials. However, we recognize that these trials have their limitations.

If we use bone mineral density as our marker of efficacy, it appears that continued drug therapy out to five years results in similar bone mineral density responses among all bisphosphonate products. When drug therapy is continued beyond five years, there appears to be a maintenance of BMD at the femoral neck and continued increases in BMD at the lumbar spine. When drug therapy is discontinued after three to five years, there appears to be an initial decrease and then plateau of BMD at the femoral neck, more decrease in BMD at the total hip, and a continued small increase in BMD at the lumbar spine.

However, in osteoporosis, it is fracture that matters. If we use fracture as the marker of efficacy, there is robust fracture efficacy with continued drug therapy out to five years. When therapy is continued beyond five years, there

appears to be at least maintenance of fracture efficacy and no clear evidence of harm.

When drug therapy is discontinued after three to five years, there is no real difference between fracture rates between those that discontinued therapy and those that remained on active drug, suggesting a possible maintenance of fracture efficacy.

As far as the question of drug holiday, data are sparse and many questions remain. It appears the best predictor of fracture after discontinuation of bisphosphonate is hip bone mineral density at the time of discontinuation. Changes in bone mineral density, as well as change in bone turnover markers after drug discontinuation, do not appear to be predictive of fracture, so monitoring these parameters may not be helpful.

Many osteoporosis experts suggest continued therapy may be beneficial for patients at high risk of fracture. However, our analysis of the small amount of data available do not suggest that

1 continued drug therapy in patients with a bone
2 mineral density less than minus 2.5 is beneficial
3 when compared to those that discontinued therapy.
4 We recognize that our analyses of this data
5 is different than what is published and what has
6 been presented today by the other presenters. We
7 looked at a composite of all osteoporotic
8 fractures, including morphometric vertebral
9 fractures and clinical fractures, whereas the other
10 analyses were done in each separate component.
11 So, in summary, we have presented all of the
12 data that we have available pertaining to the
13 duration of use for bisphosphonates in the
14 prevention and treatment of osteoporosis. Our
15 questions focus on your opinions of the evidence
16 for both the risks and the benefits of long-term
17 bisphosphonate therapy, with "long-term" defined as
18 more than three to five years.
19 When the risks and benefits are evaluated
20 together, can further recommendations be made
21 regarding what the optimal duration of use for
22 bisphosphonates is?

In addition, we welcome the panel's discussion of what other data is needed to answer these questions. Thank you.

Clarifying Questions to the Presenters

DR. CARSON: Thank you.

Now we have some time for clarifying questions to the presenters, and any questions left over from prior to lunch that we didn't get to ask the sponsor presenters.

Dr. Rosen?

DR. ROSEN: Thank you.

So I think one of the biggest issues here is the FLEX study, and we really need clarification for everybody on this. So first I'd like to ask either Theresa or somebody from the FDA to come back to a handout on page 10, which shows the nondifference in risk of fracture for women who have a T-score of minus 2.5. It's similarly on figure 8 in the printed version.

DR. CARSON: Is this the last one we just heard?

DR. ROSEN: It's the one --

DR. CARSON: Or her first one this morning?

DR. ROSEN: No. It's from Dr. Whitaker's presentation.

So I think one area of concern is we have published data showing that there are some individuals who are clearly at risk who benefit from continued therapy. On the other hand, we're hearing -- or we're seeing in this slide, and in one that's also in your handout, that there's really no difference in this sort of tendency, particularly at year 5, with only a few subjects to show an increase in continued alendronate use.

So, first of all, are these all osteoporotic fractures, or are they vertebral fractures, or nonvertebral fractures? So that's the first question. Do we have clarification on that?

DR. KEHOE: These are what we considered all osteoporotic fractures. So they are morphometric vertebral fractures, plus clinical nonvertebral fractures. It excludes fractures of the fingers, toes, hands, and skull.

DR. ROSEN: So, Theresa, if that's the case,

tell me about your analysis for nonvertebral fractures, which are all clinical, I presume. Did you do the same analysis just for nonvertebral fractures?

DR. KEHOE: We don't have Kaplan-Meiers for simply nonvertebrals. But I would note that in this analysis, most of it is being -- you're going to be driven by the largest number of fractures here, which is nonvertebral.

DR. ROSEN: Nonvertebral. Right, right.

Okay. So have you had a chance to go back and talk to either Doug or Dennis or the UCSF group about the difference in their analysis, showing that there was significant risk reduction in those individuals with a T-score of minus 2.5 without a prevalent fracture who subsequently went on to stay on treatment?

DR. KEHOE: We have not had the opportunity to discuss this with anyone else. We will certainly be taking that opportunity after this meeting.

DR. ROSEN: I have one other question, if

nobody minds.

In the other presentation on osteonecrosis of the jaw, which was also done by the FDA, and that is Dr. Kuyateh's presentation, we showed data on the PROBE study, which is the osteonecrosis of the jaw study. And I think that is figure 25, slide 25, the ONJ PROBE study.

So this gives us a potential prevalence of .1 percent for osteonecrosis of the jaw. That's extremely high. That's much higher than previous prevalences. It's 10- to a 100-fold higher than prevalences reported in other surveys.

So I need some explanation about the limitations, further explanation about the limitations. I know this was a mail-in survey, but they did bring the people back for dental examinations. So can we hear a little more about that? Because that's the only study that's really talked about in this analysis of ONJ.

In trying to get at the prevalence, I understand that ONJ is extremely hard. There's a lot of guesswork involved. But I think

representing .1 percent, or 1 in 1,000, may be a little misleading compared to some of the other data sets. So tell us a little more about the justification and some of the limitations.

DR. MCCLOSKEY: May I introduce myself? I'm Carol McCloskey, an epidemiologist at FDA and one of the principal investigators from FDA on this study. I didn't do the study, of course, but I think what is significant here that you have to understand is that the denominator was the respondents to this survey.

So the denominator is not all bisphosphonate exposures. But then, again, by nonresponders, we don't know how many of those had ONJ either. So we did just by ONJ cases over the respondents.

DR. CARSON: Thank you.

Other questions from the panel?

Dr. Collins?

DR. COLLINS: Yes. I had a question that I didn't get to before for the Warner Chilcott investigators in regard to the -- so there's slide 12. The data are presented that show the

bone mineral density effects -- or, no, the bone turnover marker effects in the off period at the months 84 through 96. But did you show us the fracture data in those two groups during thought same period? I would think that -- was that what was in slide 15? It doesn't appear to be the case.

So what are the fracture data for those two groups of patients during that period of time, that is, the final off-risedronate period, that are shown in figure 12?

DR. CARSON: Dr. Miller?

DR. PAUL MILLER: Yes. Thank you for the question. There was only one fracture that occurred in patients that came off -- that were on risedronate in that 1-year period, so just too few, a small number.

DR. COLLINS: But I mean, what's the denominator? Obviously, I guess there's no difference. But, I mean, what sort of numbers were we talking about at that period of time?

DR. PAUL MILLER: I don't have the figure in front of me. I think there's 81 patients in

each -- about 81 patients in each group by that time.

DR. COLLINS: So in slide 15, it had been 398, 361 patients, and now the denominator -- I don't understand how the denominator dropped off so quickly, then.

DR. PAUL MILLER: I'm sorry. I missed your question.

DR. COLLINS: So slide 15, I guess, then, reflects the period 62 to 84 months?

DR. PAUL MILLER: Slide 16 is a different cohort. That's the North American trial. The slide that you had before -- go back to --

DR. COLLINS: So slide 13 are the fracture data. Is that right?

DR. PAUL MILLER: Slide 13 is from the multinational cohort, from the European cohort.

DR. COLLINS: I see. Okay. All right. So the bottom line is there was no difference in fractures between the on and off groups.

DR. PAUL MILLER: Yes.

DR. CARSON: Dr. Burman?

DR. BURMAN: Thank you.

Just a point of clarification, maybe from Dr. Whitaker or from the FDA. On the slide of no vertebral fractures, for example with Reclast, you divide them up into morphometric vertebral fractures and clinical vertebral fractures.

Could you explain those a little more? In these studies were X-rays routinely taken at a periodic time frame? And if someone had a clinical fracture, did they actually have X-rays documenting it?

DR. WHITAKER: For the clinical fractures, X-rays were confirmed. For the morphometric fractures, they were done in an extension study at year 4.5 and then at year 6.

DR. BURMAN: Thank you.

DR. CARSON: Yes? Did you have a question?

DR. KITTELSON: It's me, huh?

Along these same lines, perhaps we could have slide 20 from Dr. Santora's presentation. I just want to get a sense of what I should be looking at in terms of the relative risks on

clinically important fractures. That's in the same spirit of things that have been asked before.

DR. SANTORA: You're looking at slide 20; is that correct?

DR. KITTELSON: Slide 20, yes. It gives the nonvertebral fracture risks during FLEX.

DR. SANTORA: Could we put that one up? Right.

DR. KITTELSON: So as I look at it, you've got the first set of columns there, bigger than negative 2, and the last at less than or equal to negative 2. So I guess either you or the FDA can comment on is the FDA analysis in some ways a compilation or a collapsing of the first two columns with the last two columns, and therefore showing not much effect; whereas if we split in the less than 2, and we focus on nonvertebral fractures, that this is sort of the contrast between those two.

DR. SANTORA: I believe Dr. Whitaker indicated that was a different analysis that was done.

Is that correct? It's not on nonvertebral fracture. Is that right?

DR. KEHOE: Our analysis looked at all patients with a BMD T-score of minus 2.5 or less. In this analysis, it's patients, based on their T-score, but also only those patients with no prior vertebral fracture. So we included patients with vertebral fracture as well as those without. So I think those are some of the nuanced differences of what you're seeing in the results of various analyses.

DR. KITTELSON: But it's largely that subsetting issue, I think, that we're dealing with here; correct?

DR. KEHOE: Yes.

DR. KITTELSON: Okay. Thank you.

DR. SUAREZ-ALMAZOR: Yes. Going back to that slide -- sorry, but since you're there.

Yes. Do you have the same slide for all the patients combined and not just for those who had no prior vertebral fractures?

DR. SANTORA: We don't have that

presentation.

DR. SUAREZ-ALMAZOR: Do you have the data?

DR. SANTORA: We have the data. As I said, the reason this subgroup analysis was justified was because there was an interaction between BMD, that is, in this case hip/neck BMD, and the outcome, in this case nonvertebral fractures. We didn't see that, I guess, for clinical vertebral fractures. And I believe it was looked at for all patients, if you will.

So this is the only group where we saw an interaction. I think it's the situation there this is a low-risk population. They don't have a prior vertebral fracture. And the question is, even in this low-risk population, are there patients who don't benefit and patients who do benefit? So that was the way the question was asked.

The data are there. I just don't have that particular analysis with me.

DR. SUAREZ-ALMAZOR: Well, but that particular analysis would be the first analysis that would be done with the entire group. And I

was just wondering if in that case it would be similar to what the FDA found, basically no difference, when all patients are considered and not just a subgroup.

DR. SANTORA: As I said, I can get the numbers and add them together. But when the interaction was looked for, is there an interaction between BMD and fracture outcome, you don't see the risk.

Actually, Dr. Bauer, have you done any specific analysis she's looking for?

DR. CARSON: Dr. Bauer?

DR. BAUER: I'm sorry, because I didn't present this data because I didn't know what the FDA would present. But it's actually in table 4 of the JAMA paper by Black, et al., published in 2006.

All comers, looking at non-spine fracture in FLEX, stratified by bone mineral density at the beginning of FLEX, among the women that had T-scores less than minus 2.5, the point estimate was .77 for nonvertebral fractures, with a confidence interval that extends from .5 to 1.2.

Those also looked for a full interaction among all women with the bone mineral density, and the p-value for that interaction was .40. So there was not a statistically significant interaction. There was a trend towards fewer non-spine fractures in the group overall that did not reach statistical significance.

The interaction that Art actually mentions -- although, I do want to point out that this was actually an analysis that was led and published by the UCSF group, not by Merck -- was limited to women that did not have a vertebral fracture at baseline.

Again, when you combine both the women that do have a vertebral fracture and those that do not, the overall interaction is not statistically significant.

DR. CARSON: Dr. Suarez, you had some questions from this morning that you didn't get to ask. You can ask those now. We have some time.

DR. SUAREZ-ALMAZOR: I had another question related to the presentation by Dr. Bucci. If we

could go to slide number 6.

DR. CARSON: Are we able to get --

DR. SUAREZ-ALMAZOR: Sorry, slide number 12. Sorry.

DR. CARSON: Slide number 12 from Dr. Bucci's presentation.

DR. SUAREZ-ALMAZOR: Yes. That's the one.

This is a logistic analysis that was performed just in one of the subgroups of the follow-up, and I can't remember is Z3P3 meant that they received the drug or they didn't.

But I was wondering if the same analysis was conducted in the entire group by entering as a variable whether they had treatment or not, and whether treatment was significant after controlling for all the rest.

DR. BUCCI-RECHTWEG: So Madam Chairwoman, Dr. Cosman is in the audience and this data has not been presented publicly.

Can she be recognized to speak to the data?

DR. CARSON: Yes, that's fine. Just give us your name, identify yourself and any financial ties

that you might have.

DR. COSMAN: My name is Felicia Cosman. I'm an endocrinologist and osteoporosis specialist out of Columbia University. I have relationships with essentially all the companies that make drugs that are used for osteoporosis, and I am here today on behalf of Novartis.

This study is a study in which I've been involved. I've been on the steering committee for the HORIZON trial from the beginning and have begun -- did begin this analysis about a year ago at ASBMR, and we are going to be presenting these data next week in San Diego.

What I think the importance of our study is is that the findings are consistent to a large extent with the findings from the FLEX trial in the sense that we have been able to identify some factors in a population of patients that's already been treated, in our case for three years, in the FLEX case for five years, which seemed to be predictive of patients going on to have higher risk of fractures over the ensuing three-year follow-up

period.

So we looked, just as the UCSF group did in the FLEX trial, at the group that was randomized after the initial treatment period to placebo. And we found that hip bone density was in fact a major predictor of future risk of fractures, both of the spine and of nonvertebral sites.

We also found that if you had a fracture while you were on the therapy during the first three years, that you were at higher risk of future fractures. And we found a relationship of borderline significance for new vertebral fractures, but highly significant for nonvertebral fractures if you had prevalent fractures.

This second step we did was to look for treatment effects and treatment subgroup interactions. We found that there were, for vertebral fractures, no treatment subgroup interactions.

So the treatment effect for vertebral fractures was consistent across all subgroups, whether you were high-risk based on bone density or

1 recent fracture, or whether you were at low risk.
2 However, when you look at numbers needed to treat
3 and, potentially, numbers needed to harm, the
4 numbers are much lower needed to treat if you're in
5 a high-risk group. And, therefore, we think it
6 might make sense to consider extending treatment
7 beyond the initial three years, perhaps up to six
8 years, in people who look like they're at high risk
9 where the numbers needed to treat are very low.
10 And we think it might make sense to consider
11 discontinuing therapy in people who appear to be
12 low risk even though there may still be a treatment
13 benefit, but the number needed to treat may be too
14 high to justify prolonged treatment.
15 DR. CARSON: Thank you. Would you give your
16 name to the transcriber for us, please? Just write
17 it down for her.
18 DR. COSMAN: Felicia Cosman.
19 DR. CARSON: Dr. Tucker?
20 MS. TUCKER: That's all right.
21 I was looking at Dr. Kehoe's history,
22 regulatory history, and my question to start out

with is, it says there were 4.54 million people with prescriptions in 1909 [sic]. Is that approximately the same in '10, in the year 2010?

But the point I wanted to make is, basically, that all of the statistics are one thing. People are the other. If 1 percent of these people get the atypical femur problem, that's over 45,000 people. And so I figure my position on this committee is basically to help us remember the faces of the people. Thank you.

DR. CARSON: Dr. Orza?

DR. ORZA: I have two small clarifications for the FDA folks, I think. One is, were all of the cases that were submitted for the record or presented today, were all of those included in the analysis you presented to us of cases you collected from AERS and literature and --

DR. KEHOE: We didn't actually present the AERS data today.

DR. ORZA: It was in the background document.

DR. KEHOE: It was mostly epidemiologic. I

would assume that we have done AERS analyses. And I would assume that all the cases you heard today, if the ladies are telling you that they have submitted them to AERS, they were included in those analyses if they were submitted to MedWatch.

DR. ORZA: And then the second one was, Dr. Kehoe, you also mentioned this in your earlier presentation, and it's in the background document, about the National Hospital Discharge Survey and the apparent trend for declining rates of typical fractures. But the rate of the atypical fractures is remaining stable.

So is it fair to say, then, if you put those two things together, that actually the ratio of the atypical to the typical is going up?

DR. KEHOE: That paper that I referenced also looked at subtrochanteric fractures. It did not look at atypical fractures because there's no way from the discharge summary to be able to -- survey -- to get that information. But the rate of subtrochanteric fractures has remained stable between 1996 and 2006.

DR. ORZA: So if the ones that we are fairly certain about the coding of as hip fractures are going down, and the ones that we can be fairly certain about the coding of as the subtrochanteric are not, is it fair to say that the ratio, then, of those has been changing over time, too, so that the ones that we're worried about are actually now a larger proportion than they were?

DR. KEHOE: I think that's certainly a possibility.

DR. CARSON: Dr. Woods?

DR. WOODS: I'd like to go to Dr. Hill's [sic] presentation in slide 9 that talked about the affinities of the different bisphosphonates, and just wanted to make sure that I understand this. This affinity slide, would that also imply something in the way of the time we would expect for the compounds to remain active in the body?

Then the second part of that, do you think that that would have an implication on what we ought to think about in the way of drug holiday?

DR. PAUL MILLER: Yes. Thanks for the question. I think it would be an extrapolation without data to conclude that this would translate into duration of half-lives among different drugs in the body because I think that this is an in vitro study that's very, very good science that shows how tightly they bind to the hydroxyapatite crystal, which then gives you the suggestion that those that have a lower affinity would come off faster and be eliminated faster; and those that bind tighter would come off slower and be eliminated slower, and would last longer.

Some of those theories may have some validation in the data from the clinical trials, where you can get a once-a-year formulation or once-a-month versus -- and still have the biological effect persist. But I don't think you can take that type of associations to the assumption that, for patient management, that means that five years of one versus three years of another would be sufficient, or two years of one versus six years of another, because of the

different affinities from this in vitro finding.

I think that what we don't know is that when you give a bisphosphonate, whether you give it oral or IV, how much is taken up in a skeleton? This is assuming equivalent availability in the blood. It's largely a function of the baseline remodeling space, how much remodeling is going on in that individual? So somebody with a high remodeling may take up more and accumulate more; and someone with a low remodeling may take up less and accumulate less. And until we have data that we can look at the total body burden of bisphosphonates, I don't think we can answer that question.

DR. CARSON: Dr. Johnson? Oh -- I'm sorry. Dr. Johnson?

DR. PAUL MILLER: Did you want to extrapolate on this, Graham?

DR. CARSON: Oh, did you? Oh, I'm sorry. I didn't see that.

DR. WOODS: I had a follow-up and then another question. The reason I asked that, I guess, is that if this kind of data were to hold

1 true with total body clearance, then I think there
2 would be implications for which of these agents you
3 might want to select for an elderly patient, who's
4 more predisposed to fall and consequently could
5 clear the drug from his system. So thank you for
6 your answer.
7 My second question relates to something that
8 was in the McCloskey review related to the PROBE
9 trial, and the recommendation of the American
10 Association of Oral and Maxillofacial Surgeons.
11 And then you also talked about the upcoming
12 publication in the Journal of the ADA related to
13 holding these medications after dental surgery.
14 Dr. Bunning and Dr. Schneider also talked a
15 little bit about delays in wound healing and some
16 of the things that they'd seen in their clinical
17 practice.
18 Is anyone aware of any studies that
19 demonstrate these agents do lead to a delay in
20 wound healing or the healing of bone? And, if not,
21 I guess it would seem to me that would be a really
22 important question to get our arms around later.

DR. BUCCI-RECHTWEG: Yes. Actually, to the other side of that. So with the Reclast recurrent fracture trial, these are all patients who were enrolled who had incident hip fracture.

One of the categories that was looked at prospectively through adjudication was, in fact, male union/nonunion. And between those patients who received Reclast annually and those patients who had received placebo, there was no difference in those events, in a well-controlled prospective trial, all patients who had had hip fracture.

DR. CARSON: Now, Dr. Johnson.

DR. JOHNSON: Well, let me bring back again Dr. Miller. I just had another question about the data that you discussed regarding the VERT North American trial.

You described -- and this is from the final report -- that there appeared to be an increase in new vertebral fractures in year 4 when they were off of medication, when they were on placebo.

Can you tell me what is the difference between the medication and the placebo? Is that a

significant difference?

DR. PAUL MILLER: Between the treated and the untreated group, the p-value was .33.

DR. JOHNSON: Okay. And there appears to be a decreased number of nonvertebral fractures in the placebo group. What was the p on that?

DR. PAUL MILLER: That was nonsignificant.

DR. JOHNSON: Thank you.

Can I ask one more question? And this is for the Novartis group.

I know we didn't talk about it today, but there has been observational studies that have suggested an increase in ONJ in individuals with cancer. Is there some acceptance that ONJ is more likely in individuals on IV bisphosphonates who have cancer, and would that not potentially relate to non-cancer patients?

DR. BUCCI-RECHTWEG: I'm joined today by my colleague from the oncology group who can address your question specifically related to the use of zoledronic acid in oncology.

DR. SAUTER: Yes. Hi. My name is

Dr. Nicholas Sauter, and I work at Novartis for the Zometa. So I'd like to hear the question again.

DR. JOHNSON: Yes. There are three observational studies that indicated a four- to fivefold increased risk of osteonecrosis of the jaw in individuals who -- that was associated with IV bisphosphonate use. So just to confirm that that appears to be a potential risk, and why that would not apply to non-cancer patients.

DR. SAUTER: Okay. So the first thing I wanted to say was that it might be prudent to be careful about extrapolating between what's observed in the safety of cancer patients receiving Zometa, and safety data that is occurring in osteoporosis patients that are getting oral or IV bisphosphonates.

For example, Zometa is used for patients with advanced malignancy. They have bone metastases or multiple myeloma. They're getting treated at 4 milligrams every three to four weeks, compared to 5 milligrams once a year in Reclast. And the entire disease process in bone is

fundamentally different. So in bone metastases, you have malignancy in bone that's destroying bone and disrupting bone remodeling; whereas in osteoporosis, there's a different process going on.

Similarly, the life expectancies are different in the two populations, and other comorbidities and other medications that are being taken and therapies that are being taken impact the risk of these events.

So I don't know. Does that answer your question or do you still want -- do you need more clarification?

DR. JOHNSON: No. I think that's sufficient. Thank you.

DR. SAUTER: Okay. Thanks.

DR. CARSON: Final question. Dr. Nelson?

DR. NELSON: Thank you. Actually, this question is for Dr. Miller, if that's okay. I guess just try to put some biological plausibility on some of these issues and maybe help me understand some of these things.

But as I understand it, the femoral neck and

the hip itself are largely trabecular bone, and the subtrochanteric region is pretty much cortical bone. And we know that the bisphosphonates seem to improve the strength or the mineralization of the hip, but they seem to weaken, I guess, the mineralization or at least the function of the cortical bone. That's the bone that should be pretty strong in the mid-femur.

Is there any mechanism that you can provide that would allow this to be explained? I mean, why would that happen? And I guess the corollary to that is, if there is a reason, is there a subset of patients who we may be seeing now who are the early presenters with this therapy who they're the ones that break at five or six years of therapy, and if we run this therapy out 10 or 12 or 15 years, we're going to start to include more patients in the atypical femur fracture group?

DR. PAUL MILLER: Let me think. Bisphosphonates improve cortical bone strength, and they do so by a number of different mechanisms. I mean, part of it's related to reduction in bone

remodeling. A lot of it has to do with the fact that bisphosphonates reduce cortical porosity, and by reducing cortical porosity, the strength goes up.

So when you look at different biomechanical testing of the strength categories and ways of testing the strength of the femur, or whether it's the shaft or the femoral neck, you'll see the bisphosphonates in animal models, whether it's finding that element analysis in human models, increases the strength of that in those areas.

So there's no biological mechanism that we can explain at the current time of the theory of how a subtrochanteric shaft might be compromised by a bisphosphonate. There's a lot of theories. I could sit here and hypothesize with you. I'd love to do that, but --

DR. NELSON: So I guess my question is, you know, there's a difference between function and mineralization. So I agree that they probably increase mineralization, but does that necessarily mean -- because bone turnover is slowed. So if

there were micro-traumas to the bone which don't really remodel over time, which would normally remodel, would that be an explanation, perhaps, why this would occur?

DR. PAUL MILLER: Mineralization goes down with bisphosphonate. The mineralizing surface is reduced. But mineralization doesn't get turned off. You can still see on bone biopsies. And all the bone biopsy data -- and Dr. Recker, who's one of the world's experts, is in the audience -- you'll still see mineralizing surfaces and single labels on these biopsies at different scaleable sites in this population.

In fact, if one of the theories behind the mechanism of impairment in bone strength and postmenopausal osteoporosis is fundamentally a higher bone turnover, because turnover goes up as we age, one of the mechanisms therefore by which bisphosphonates improve the strength of the bone is by reducing mineralization, but it doesn't shut off mineralization.

DR. NELSON: BMD is mineralization. It's

the density of minerals, isn't it?

DR. PAUL MILLER: Well, the two-dimensional DEXA, there's a difference between the histomorphometrist, that way of evaluating mineralization and mineralizing surface and two-dimensional DEXA. Bone mineral density equals bone mineral content divided by the area. It's really not a true mass, true mineralization measurement.

DR. CARSON: Okay. We'll forego our break and have Dr. Rosen ask one more question.

DR. ROSEN: I have a question for the FDA which I want to thank the people who testified for raising it. And that's the bigger question, which I think we're all going to have to deal with, is how did we get an indication for osteopenia when, in fact, we're all talking about patient-specific outcomes such as fractures?

So, Theresa, maybe you can enlighten me a little bit on the history behind the indication for a bone density surrogate marker.

DR. KEHOE: Well, there isn't actually an indication for osteopenia per se. If you cast your

mind back to 1995, the world of osteoporosis was fairly different back then. And so the way the trials were designed is that the pivotal fracture trials looked at patients who had low bone mineral density and a prevalent vertebral fracture. And that was the treatment of osteoporosis indication. And the prevention of osteoporosis indication were those patients that had osteoporosis by BMD but had not necessarily fractured. So that would be more a primary and a secondary prevention type of indication. Some of the industry representatives may have a better understanding of this since this preceded my time.

So that's, I think, where we got into the two indications that we currently have. Over the years, I think most in the bone community recognize it became more and more of an issue, the ethics of having these fracture trials. And so it no longer became ethical to enroll patients that were osteoporotic and had a fracture because there were available agents out there.

So what we have seen in the fracture trials

is that we are enrolling patients based on bone mineral density alone. And so there's sort of been a shift change, and where the prevention indication has also shifted in concert, that it's actually people with low bone mineral density.

DR. ROSEN: So I guess my question, though, is when we talk about prevention of osteoporosis, you commonly hear people say that an indication for using these drugs is osteopenia.

Is that correct or incorrect?

DR. KEHOE: I would imagine that's technically correct, but I think that, unfortunately, the indications have preceded where the standard of is in the field now, which is that a prevention indication, I think, is really being revisited all the way around, including by FDA.

DR. ROSEN: Yes. That's what I wanted to hear. Somebody's looking at --

DR. KEHOE: Well, I think that might be a topic for later, later advisory committees. But certainly it's something we're struggling with in dealing with.

Questions to the Committees and Discussion

DR. CARSON: Okay. Thank you.

We're now ready to begin the panel discussion portion of the meeting. And we have five questions, one of which is a voting question. That's the last. No, sorry, six questions. And question number 5 is actually a voting question; all the others are discussions.

So we'll take roughly 15 minutes for each of these discussions, and I will try to summarize after each question. If we get moving quickly, then we might be able to have a break. But I think maybe if you need to have a break, you can each individually go in the next hour and a half.

So let me read question number 1 as we display it. Please discuss the strength of the available evidence that suggests that the safety concerns outlined below are associated with long-term, that is, greater than three to five years, use of bisphosphonates: atypical subtrochanteric and femur fractures; osteonecrosis of the jaw; esophageal cancer.

So why don't we take that question for each of those individually and begin with atypical fractures. Any comments on the strength of the available evidence suggesting the safety concerns with long-term use? Dr. Johnson?

DR. JOHNSON: I wonder if perhaps a reason no one jumped ahead with speaking on this is that the data is so limited. We really have relatively minimal data on looking at this. And if you look at the reports from each of the companies, their data from their studies do not really provide us the information that we need.

I think it was fascinating that there was a group put together online that came up with the 111 patients, and I think that was a good piece of data. But I think we need to continue to get epidemiologic data and look at the risks for more than three years, more than five years, and see what these risks are.

I mean, this is a concern. This is an unusual fracture. It was something that was not initially considered as a potential concern with

these medications. Clearly, there is benefit with typical hip fractures, but to see these atypical fractures cropping up certainly raises the concern that I think another member said earlier, that this is just the beginning of what's going to prove to be a long-term concern.

So I definitely think we need to have the data to know what the risk is so we can cancel patients. I'd say at the current time, we can tell them we don't yet know but we have concern, but that's insufficient. We need to be able to understand this more fully.

DR. CARSON: Dr. Cooper?

DR. COOPER: In terms of thinking about the strength of the evidence, certainly the comments from the public representatives were compelling and provide information for us to begin to think about what might be going on.

In the FDA briefing documents, they described the establishment of stricter definitions for these atypical femur fractures and provided information that suggested that applying those

definitions to epidemiologic data would suggest the potential for a stronger association. So what I would say is that I would describe this as emerging data that needs further follow-up.

DR. CARSON: Dr. Gut?

DR. GUT: Like Dr. Johnson and Dr. Cooper, I think that strengths of evidence is very poor to confirm these safety concerns. And I would refer us to the slides presented by FDA presenter, one that was clearly stated with regard to a typical fracture, that relationship with duration of the use is unclear and causality are certain. Thank you.

DR. CARSON: Dr. Madigan?

DR. MADIGAN: I agree with these comments that the evidence is obviously not crystal clear, but in the two long-term -- the Park-Wyllie study and the Schilcher study, the relative risks are substantial for long-term use.

I would just make one other comment. On the Kim study, data have a relative risk for five years -- this is in the FDA briefing

1 document -- for greater than five years usage. And
2 that was characterized as no association. Well,
3 it's not. It's a relative risk of 2. It's not
4 statistically significant, but I would not -- to
5 dismiss it as no association seemed not appropriate
6 to me.
7 DR. CARSON: Dr. Nelson?
8 DR. NELSON: I think the epi data is weak,
9 obviously. But I'll go back to what I had kind of
10 tried to bring up before, which is this is
11 obviously an atypical fracture because it's
12 atypical. It seems to be occurring in this group
13 of people, and it doesn't really occur in anybody
14 else, at least to the atypical fractures we're
15 talking about.
16 Where I was trying to go with the biological
17 plausibility issue is to establish -- causality may
18 be a strong term, but at least some association,
19 maybe, that there may be a mechanism that this is
20 actually occurring is some new perhaps
21 understanding we need to have about how bone
22 remodeling occurs and how these drugs specifically

work. Because it's just not totally clear to me that having more density, or mineralization, or whatever the term is, is necessarily a good thing. It might seem like it would be, but I'm not sure we definitely know that. And we really have to differentiate those two forms of bone because the bone is just not one very simple organ, obviously. It's very complicated.

So it may not be the answer you're looking for, but it's just a thought.

DR. CARSON: Dr. Morrato?

DR. MORRATO: Yes. I just wanted to echo what Dr. Madigan was saying and just build on that. I think what was striking to me is when you actually peeled the onion and started to look at the epidemiology studies, you could see the various limitations. And it calls back to the need for I think a more definitive study, and a couple of the points that were mentioned earlier; part, sample size. But I think what was striking is that in some of the studies we're looking at radiographic evidence, which is a better case definition that's

needed.

The other piece that really wasn't adequately addressed in the earlier studies was the duration of use. So if we go back to what was shared earlier in terms of the drug utilization, that only 10 percent of patients are making it out to three years of use, you would expect that in these cohorts of retrospective data of clinical populations, a small group is probably getting to that range in which you might pick up some of these adverse effects.

So I think that would be another piece that would be useful to look at moving forward in epi studies, is to get better radiographic evidence and chart review, et cetera, and have a better handle on the duration of use.

DR. CARSON: Are you just limiting your comments to atypical fractures or are you --

DR. MORRATO: Yes.

DR. CARSON: Dr. Collins?

DR. COLLINS: Yes. I just wanted to echo -- I was searching for the word to describe

this, and I think the evidence as emerging is a good descriptor. I think probably for an epidemiologist, this is not very good data. But if you go to clinicians, if you go to orthopedic surgeons, they're absolutely convinced of this data. They never saw this before, and now as a group they see it a lot.

It reminds me of the early days of the AIDS epidemic. They never used to see Kaposi's sarcoma, and all of a sudden it was emerging. So I think -- and I applaud the FDA. I think we're on the leading edge of this, and I think we need more research. And the one thing that I would advocate is more basic science clinical research to try and get at the mechanism, to look at the bone, to look at the patients, the bone from the patients who are having these sorts of fractures, to see what we can learn more about it.

DR. CARSON: Dr. Orza?

DR. ORZA: I was thinking that in terms of the larger scheme of things, that after so many years and so many millions of patient-years of

experience, that it's a pretty sorry state of affairs to be dealing with data of this nature.

So I think that this is a little bit of a cautionary tale for when we find ourselves dealing with surrogate endpoints and when we find ourselves extrapolating long-term treatment from short-term data. And I think it also bolsters FDA's enthusiasm for using all the news tools it's been given, to do more on the safety side of things and on the postmarketing side of things.

But all that being said about how disheartening these data are, I think maybe we can't say that there is clear evidence of causality, but it seems to me that in the scheme of things, it's a relatively strong signal. I mean, I don't know how it stacks up against the other kinds of signals that you see, but it seems like a pretty strong signal and one that can't be ignored, and one that maybe can't be pushed off by saying, we need to do more studies. We need to get better data. But in the interim while we're doing that, we need to do something about the signal.

DR. CARSON: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Yes. Two points I would like to make. When looking at more and higher quality data on this topic, I think it is going to be important to look at the absolute risk and not only the relative risk to put these factors into the context of the other factors that we might be preventing long-term.

The relative thing is that we have seen some data on what can happen if you discontinue after three or five years for other factors. But I think with the data we have seen, we cannot know whether discontinuing is going to reduce the potential association with these atypical fractures. So we also need to see whether that's going to help, discontinue after three or five years.

DR. CARSON: Dr. Vaida?

DR. VAIDA: Yes. I'd just like to echo a couple other of the comments, too, on this in that the strength may not be totally there, but I really think that from the information we've received and also that's been given to us, that there certainly

is an association with this. And I know you're just focusing on the first one, but it's almost like if you were asking to rank them.

I mean, this is one where I feel that, if I had to use the word "strength," is there even more so than others.

DR. CARSON: Ms. Tucker?

MS. TUCKER: Drs. Miller and Dr. Russell were talking about the fact that there are people who are in clinical trials, and then there's the rest of the general population. Well, this seems to be a problem that's occurring much more in the general population.

So from my perspective, it just means that anything that's designed to help get the figures needs to be able to have as much participation as it possibly can.

DR. CARSON: Okay. Let's move on to osteonecrosis of the jaw. We've already talked about atypical fractures. Any new light to the either more firm association with ONJ or less concern? Dr. Burman?

DR. BURMAN: Thank you. I think the data again are relatively weak, and we have to make extrapolations. But there was the retrospective study, the survey study, that showed there was a .21 risk for ONJ when patients took it for more than four years, whereas it was only .05 when they took it for about two years. So I think there is perhaps a little more information relative to duration.

DR. CARSON: Yes, Dr. Erstad?

DR. ERSTAD: This is one that for me, for future research, it seems like if there was a focus in the dental area, of invasive dental procedures being performed. We're sort of trying to get at it from another way from the general physician's accounting for these. And it seems like if we specifically go after that group from an epi standpoint, we might be able to pick some of this up.

DR. CARSON: Dr. Cooper?

DR. COOPER: There's one slight difference for this question, and that is the fact that in the

doses used for cancer-related treatment, there does appear to be a relatively strong association. And, therefore, you would think about, though we don't know the mechanism, that continued exposure to this drug for longer periods of time would seem to potentially -- if it's a sort of a dose-related response might be a possibility.

So that's one difference that would apply when I'm thinking about what the strength of the association is here.

DR. CARSON: Dr. Nelson?

DR. NELSON: I was just going to try one more of my standard biological plausibility issues. But, historically, one of the few causes of necrosis of the jaw was elemental phosphorus. And this is obviously an analog of phosphorus, and it certainly makes sense that there is some potential for that type of molecular mimicry, if you like that term, or crossover.

DR. CARSON: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Yes. I agree with Dr. Cooper in that we have some kind of

plausibility because of what we know with the higher doses used for cancer. On the other hand, here we might be talking about something happening in 1 in every 10,000 patients versus a higher potential incidence of the atypical fractures.

DR. CARSON: Dr. Rosen?

DR. ROSEN: Yes. So I think, unlike subtrochanterics, I think we're seeing a lot less ONJ than we are subtrochs. And there is a dose-response, and I agree with you. I think the question is, is it adequate enough? Is it high enough in the osteoporotic patients. And, clearly, we're not seeing that kind of frequency that we are with subtrochanteric fractures.

So we clearly need more data. The mechanism is not known. It's not known for subtrochanteric fractures at all. There's lots of possibilities, but I don't think anybody really truly understands it.

So I would agree that there is a dose response, so there might be a mechanism. The real question is, do you ever reach that threshold of

dose response with osteoporotic patients?

DR. CARSON: Dr. Kittelson?

DR. KITTELSON: Yes. I agree with most of the comments that have been made. A particular mechanism I worry about, we don't know if it's something with the remodeling process that's not allowing any damaged bone to heal in some way, which not throw one out.

So that would also call to mind, we don't necessarily know time frame. This question is built around longer than three to five years or that kind of thing. So I think we can certainly come up with cases, and probably a series, where bad things happened much earlier. So the time issue in there in both of these cases, I think, is of concern.

Second is it's not just these kinds of -- not necessarily the atypical fracture or even necessarily osteonecrosis of the jaw. There may be other things that should be looked at in this same light once we have a better understanding of what mechanism might be. That's what I'd add.

DR. CARSON: Let's move on just to the esophageal cancer. Comments? Dr. Rosen?

DR. ROSEN: No data.

DR. CARSON: Yes?

DR. WINTERSTEIN: I agree, no data. But there are two studies. There was the discussion that these studies might contradict each other because one finds no risk, the other one finds a risk. Looking at the confidence intervals, they actually don't contradict each other. They actually include each other.

What I thought was alerting in this was that in the case-control study, there was also an estimate for long-term exposure, which is this restriction to more than 10 prescriptions, and this confidence interval doesn't overlap any more for the study that found no risk. In contrast, this confidence interval is reasonably supportive that there is a risk.

The other issue here is that there is also biological plausibility for a mechanism. So from that perspective, I do remain concerned about this,

1 despite no data.
2 DR. CARSON: I'm sorry. I didn't
3 quite -- are you saying you do feel there is enough
4 evidence to suggest that there is an increased risk
5 of esophageal cancer, or you're saying there's not?
6 DR. WINTERSTEIN: Yes. I mean, usually you
7 would want to find a safety study, an
8 epidemiological safety study, controlled by another
9 epidemiological safety study. In this case, we
10 don't have this. But at the same time, we cannot
11 really say that these two studies contradict each
12 other because the core study has a fairly large
13 confidence interval, which includes the confidence
14 interval of the study that finds the safety issue.
15 So from that perspective, the power is just
16 not good enough to really differentiate among those
17 two. So at the end of the day, the way I'm looking
18 at this is, we do have in one of these analyses a
19 restriction to long-term use again, which was those
20 10 prescriptions, a minimum of 10 prescriptions of
21 bisphosphonates.
22 In this analysis, we have a relative risk of

1.93 with a confidence interval of 1.37 to 2.7. So that looks like there might be really a concern. Of course I would love to see this confirmed, and maybe we get the Scandinavian data at some point that might help us find this. But I would not conclude that there is no concern for risk, based on what we have here.

DR. CARSON: Any other comments about esophageal cancer? Dr. Burman?

DR. BURMAN: Just one. I agree with the comments, but I think we should focus and have studies further on conditions that predispose to esophageal cancer, like Barrett's esophagus or achalasia, as a subgroup or a perspective study because they might be at higher risk.

DR. CARSON: You mean predetermining factors?

DR. BURMAN: Especially those, yes. Thank you.

DR. CARSON: Dr. Vaida?

DR. VAIDA: Yes. I was just going to echo that same thing. It looks like there's some here,

1 the pharmacology, would make it what the drug does.
2 But, if anything, it may just help identify those
3 people that are at risk. You've seen that with
4 smokers or COPD or whatever. I'm not sure if it's
5 so much this is in the major population, but it may
6 just identify people at risk down the road.
7 DR. CARSON: Okay. Let me summarize what I
8 think you all have said, and please feel free to
9 correct me if you don't think this captures the
10 spirit of the discussion.
11 The panel has expressed concern that there
12 is emerging evidence of association with dose and
13 duration of use of bisphosphonates with atypical
14 fractures and with osteonecrosis of the jaw. In
15 addition, although the evidence is less compelling,
16 there is some concern of a possible association
17 with esophageal cancer.
18 However, the panel feels that longer-term
19 surveillance is necessary for all of these
20 disorders, in particular, looking at the background
21 risk of all three, the duration of use and dose of
22 use with the bisphosphonates, as well as other

predisposing risks, especially with esophageal cancer, that being -- well, we could just say other predisposing risks.

Anything else to add to that? Dr. Johnson?

DR. JOHNSON: I'd just like to echo what others have said, that we really need to understand the mechanism, and we should encourage studies that look at why these events may be occurring, and look at the physiology of bone.

DR. CARSON: Thank you. Let me add to that summary that any basic science investigation regarding the mechanism of use would be strongly encouraged and highly valuable in determining not only the mechanism of action with these disorders, but also others that might be associated.

Dr. Collins?

DR. COLLINS: I was just going to echo the same point, but in addition to basic science, translational science, where we actually look at the patients.

DR. CARSON: Okay. Add that.

All right. Let's move to question number 2.

Please discuss whether the data presented support the effectiveness of long-term, greater than three to five years, use of bisphosphonates. Does this apply to all patients undergoing treatment for osteoporosis or to a subset of patients, such as patients with a T-score of less than minus 2.5 and/or a prior history of fracture?

Dr. Orza?

DR. ORZA: I would echo what Dr. Rosen and what so many of the people who talked during the open period, and also a large number of the people who submitted comments to the file, said about dealing with the -- this is phrased in terms of treatment for osteoporosis. But the other thing that's all tied up in there, starting with when you read the label for what the indication is, it always says, "prevention and treatment." And I feel like to not be looking at whatever the heck is meant by prevention of osteoporosis -- if we don't look at that and sort that out, and maybe even go all the way to talk about whether or not we should change what the indication is, we're fixing the

plumbing on the Titanic or something akin to that.

DR. HOEGER: And I would echo what we talked about with respect to the first three complications, that what we have is a little bit of variability between what data was presented in terms of subset. So even if we're talking about a subset, we have to look at what subset we're talking about; do they have fractures during the pretreatment part; do they not have fractures?

We never even discussed this during the interim, but are there gender differences? Obviously, 75 percent of the individuals -- and I'm assuming most of them in the FLEX trial -- was all postmenopausal osteoporosis, but that data wasn't even available.

So we have to, I think, clarify the question a little bit as to what subset, since we have two different discussions from FDA and the pharmaceutical companies.

DR. CARSON: Dr. Kittelson?

DR. KITTELSON: Thank you. Exactly. So I think there's good evidence that -- depending on

how you look at the FLEX data in particular, there is evidence that it is beneficial, longer-term use is beneficial, even when averaging over the atypical hip fractures, which would have come into that mix there.

I think that other forms of trying to risk stratify are probably really important and to follow up with that, not necessarily just bone mineral density, but there's also other scoring systems, World Health's scoring system that might provide better sensitivity and specificity for trying to identify which population should be treated.

DR. CARSON: So you're saying this is for all patients or just for the patients with a T-score less than --

DR. KITTELSON: Well, from the data we've got, I think just the T-scores less than 2.5. However, there may be other ways to risk stratify that are better at finding the people who really need this.

DR. CARSON: Dr. Rosen?

DR. ROSEN: No, I would tend to agree that there's fairly good evidence that there is a subset of individuals, depending on how you do your analysis, whether you use total hip or femoral BMD. And that's one of the differences between the UCSF and the FDA analysis.

So I think we can identify a subset of individuals that may benefit. And it's worth considering thinking about other options for doing that, such as devising a score that compiles previous fracture, change in bone density. Somebody asked the question today, one of the panelists, what about the people between minus 2.5 and minus 3.5? Those individuals should be considered in this as a gradient of risk rather than just saying, everybody lower than minus 2.5.

So I think there's potential for ways to get at a scoring or a risk predictor that might help us. But I think there's certainly a signal that there are some people who could benefit, both in the Reclast study and in the alendronate study.

DR. CARSON: Let me just comment, have a

personal comment, in that I do also myself wonder about these patients who are in these studies who are also taking other steroids. It wasn't really looked at as to how many patients take periodic glucocorticoids, how many patients take periodic testosterone therapy. They take over-the-counter DHEA.

I'm not really sure what this is doing to the binding of other drugs and, really, to osteoporosis itself, and that is somewhat, I think, concerning with all of these.

Dr. Johnson?

DR. JOHNSON: I actually really appreciate the fact that the pharmaceutical companies, several of them, had done ongoing studies and tried to look at what happened when they went off the medication and onto placebo, and began to look at that although that data was still very limited.

I would say that these studies were done for three years, and that's what was required. We really need to have studies that go much longer if we're really going to know the benefit for long-

term use. But when patients are placed on this, they're not placed for the three years of the study, as some of the individuals testified; they're told this is a treatment for life. I think we need to be really cautious as we look at this. We really need to know what the length of time is.

The other thing I would look to the FDA for is each of these medications is likely to be different. How they're -- I shouldn't say "broken down" because they're not, but how they're excreted is going to be different. How they act in the bone is going to be different.

We really need to know for each of these preparations, rather than looking at it as a class, do we want to look at that for some, yes, you need to take it on an ongoing basis to maintain bones, but for others, you really can take off a period of time; then how are we going to test for how long you can be off of it, but then before you come back on to prevent further risk of fracture.

But I really think that longer studies are really what is needed to look at long-term use

because we're talking about people are going to live 30 years after starting their medications. How many of those 30 years do they need this medication?

So I really think that the initial studies showed prevention of fracture for three years, but they didn't show what happens when you continue it for 10, 15, 20 years.

DR. CARSON: Dr. Madigan?

DR. MADIGAN: In terms of the evidence vis-a-vis fractures and long-term use, it's incredibly modeled. So the FDA's analysis shows, if you look at all fractures, there's no benefit. And if you look at the -- with alendronate, there's some suggestion of a benefit with clinical fractures. And then when you look at Reclast, there's nothing in the clinical ones, but it's in the morphometric ones, which is the exact opposite of alendronate.

Then similarly, with the predictive analysis that Dr. Bauer presented, there didn't seem to be -- there's no suggestion that reducing BMD, which is presumably what the treatment would do,

has any effect on fractures.

So all I'm hearing is the one thing is this subgroup analysis, where it's a very specific subgroup picked, and there's some suggestion that this was part of a planned analysis. But nonetheless, the only substantial evidence I'm seeing is in the FLEX study with the people with no previous fracture and less than minus 2.5.

So it seems to me the evidence is very slender in terms of fracture.

DR. CARSON: Dr. Suarez-Almazor?

DR. SUAREZ-ALMAZOR: Yes. I would agree with the comments just made. And I would like to stress again that a lot of the data that we saw today was for the first components of the trials that were three years, and there's no doubt whatsoever that these are very efficacious drugs that can reduce fractures and can reduce mortality during the first three years of treatment. And, in fact, there are probably many patients who should be on bisphosphonates and are not receiving them.

But that's not what we are discussing today.

We are discussing the data after three years, and I'm not convinced at all that there is any good data that shows that even for subgroups of patients, they should be continued. And part of that is because when all of the data is pulled together, as has already been mentioned, the FDA found no benefit whatsoever. And when we look at the individual drugs, for two of the drugs we don't have data, and for the other two, the subgroups that were analyzed were very specific and differ from drug to drug.

So, again, I'm not convinced at all, and I respectfully disagree with the comments of some of my colleagues that there is good data for subgroups. I'm not convinced about that.

DR. CARSON: Dr. Burman?

DR. BURMAN: Thank you.

I agree with what's been said. But I want to emphasize that I agree we should look at each drug individually and just say bisphosphonates across the board may not be appropriate, and we may not have the data to do that at the moment.

But, in addition, the question, as raised, is what about the effect more than three to five years? And in my mind, there's a difference between 5 and 10 years and greater than 10 years. There's zero data that I'm aware of, or very limited, that anything greater than 10 years should be used to support efficacy versus side effects. And we're really focusing on 5 to 10 years, and there are some studies that have looked at those, and we've talked about those today. I think that's a much greyer area. But anything more than 10, of course, would be difficult.

DR. CARSON: Okay. Let me summarize. It seems to me the committee feels that the data presented do not address the efficacy of long-term use, at least greater than three years of bisphosphonate use, and that more data is certainly needed to address this question.

Specifically, the committee felt that subgroup analysis would be helpful in determining which patients would benefit by use and that each drug should be addressed individually.

The committee also felt that efficacy was seen for patients with a T-score of less than negative 2.5 and a prior fracture history, but the data was less compelling regarding all fractures, and that there was stronger opinions voiced for no efficacy when looked at overall all fractures.

Dr. Suarez-Almazor?

DR. SUAREZ-ALMAZOR: No. Actually, I think what you read was that the data of minus 2.5 was in the subgroup with prior vertebral fracture. But I think it's in the subgroup with no previous fracture, which makes it a little harder to understand.

DR. CARSON: Yes. Let me correct that. So it would be the subgroup with a T-score less than 2.5 and no fracture. Right.

Dr. Collins?

DR. COLLINS: I think you left out one of the points that Dr. Burman made, is that there is some limit to this, that we shouldn't think this is a lifetime treatment that just can go on forever. We think there's some association between the dose

and the risk, that there has to be known that probably the longer the treatment, the greater the risk.

DR. CARSON: Yes. That's true. But that wasn't really asked. That wasn't really asked in the question. But the idea was that we do need longer-term studies greater than three years.

Yes?

DR. ROSEN: Sandy, I think you did a great job summarizing. I just want to make it clear that there was not a subgroup analysis of clinical vertebral fractures in the Black study. There was a 50 percent reduction in clinical vertebral fractures from year 5 to year 10 in those individuals who were treated with alendronate versus placebo.

So I would agree with my statistician colleagues that subgroup analysis is not the best way to approach this, but there were data that there was 50 percent reduction in those individuals with clinical vertebral fractures.

So I just wanted to be sure to set the

record straight, that there is some evidence, without subgroup analysis, of efficacy.

DR. CARSON: I thought your point was to look at all groups and look at the subgroup analysis and define it further. What --

DR. ROSEN: No. The only point I was just trying to make was just that independent of subgroup analysis in the initial FLEX trial, there was clinical vertebral fracture reduction of 50 percent. That was independent of T-score or any subgroup analysis. That was purely clinical vertebral fractures, 50 percent reduction.

DR. CARSON: Okay. Let's move on to question number 3. Please discuss the overall risks and benefits of continuous long-term use, greater than three to five years, of bisphosphonates.

Dr. Erstad?

DR. ERSTAD: Well, even though I'm used to dealing with ambiguity in the clinical setting, this sort of raises it to different heights in the sense that I think we're trying to get -- we're

always trying to look at a number needed to treat versus a number needed to harm. And, ideally, we would have good numbers for both.

Even as we seem to get a little refinement under the number needed to treat, it seems like we're raising almost more questions regarding that number needed to harm. And I guess my biggest concern is that the data that we do have are from well-controlled trials or follow-ups of patients in those well-controlled trials.

It's this small percent of people in the trials, compared to the large numbers of people outside of the trials, that I think is the dilemma because, ultimately, what's happening in all of those masses of people outside of the trials. And especially if we start to increase the use of it across the board, that will just simply increase the numbers that are being treated for not all the appropriate indications, et cetera.

So, again, I have concerns with just trying to come up with that balance of a number needed to treat/number needed to harm over that longer period

of time when it's used especially in the general population.

DR. CARSON: Dr. Morrato?

DR. MORRATO: Yes. I just wanted to add to the last summary of question. I don't think you could see us here. I just wanted to build on the point Dr. Rosen was saying, that I think there are some subgroup signals, but there don't appear to be consistent signals across the trials and drugs. So depending on how you look at that, you can say there's something there or you can say they're balancing each other out.

DR. CARSON: Thank you.

Dr. Winterstein?

DR. WINTERSTEIN: Yes. I have kind of a similar comment, actually. I've tried to approach this similar to how one would approve a new drug. I mean, essentially we are discussing whether we would approve long-term use or whether we consider the risk/benefit ratio to be beneficial or positive.

The requirements for efficacy to establish

benefits so far are not met. A subgroup analysis is usually not considered appropriate to establish efficacy, and this is how I would look at this data at this point. And at the same token, I think that our previous discussion reflects that there is some true concern for risk.

So given that, I think the risk/benefit evaluation so far would not be considered appropriate or positive, given that the data is insufficient to establish efficacy, and concerning enough to raise a safety problem.

DR. CARSON: Dr. Orza?

DR. ORZA: I think there's a piece of the question missing because we can't really talk about the risk/benefit equation unless we're talking about it for a specific population. And so it should be, what do we think the risk/benefit tradeoff looks like in different groups? But one of the things I think that's necessary for considering that is some sense of what the alternatives are. So for people with genuine osteoporosis at high risk of fracture, what are the

alternatives to bisphosphonates after three years or five years or whatever?

DR. CARSON: Dr. Kittelson?

DR. KITTELSON: Yes. So, yes, how long are we really talking? The other thing is subgroups in a clinical trial have a different sort of connotation, like can't we find a genotype where this has worked and therefore should approve it. And in some ways we're talking about a distinction that was raised earlier in terms of are we really talking osteopenia or osteoporosis here? And has it really sort of been -- it's not an indication creep; it was a formal thing.

So I would just not -- I would rather not have the previous discussion of subgroups be lumped into the bin with, oh, that's bad practice in clinical trials. I think we have a different setting here when we're talking about a safety issue and an effect in trying to find populations where there does seem to be some benefit and therefore some need to be able to identify those populations better, more from the

osteoporosis/osteopenia question.

Maybe I'm a little off-topic on this one, but --

DR. CARSON: Dr. Morrato? Oh, I thought you had another question. Sorry.

Dr. Nelson?

DR. NELSON: I think benefit -- we've discussed a lot about benefit. And, obviously, in a way, the worst that could happen is that the drug won't have any benefit in the long term. And that seems to perhaps maybe where we're going with this, that the benefit does fall off, at least in the general population.

I'm still concerned that risk is a moving target. I think we have very little insight into risk. And per one of my earlier comments, which I don't think we really addressed, which is we're not really understanding what is going on. I'm still not sure that we are seeing the full risk picture when it comes to any of these issues, given the fact that, as somebody commented earlier, cancer has a 15-year lead time and the fact that there are

probably people, populations, that are sensitive or more sensitive to the fractures and other risks, perhaps, who are presenting early with these issues. And if we left the general population on this medication for more and more years, carrying it out 10 or 15 or 20 years, we might actually see not just the same number of atypical fractures or other issues, but perhaps a much more growing population, kind of a bell curve, in a way. And we're just at the very distal end right now, and we don't really know where we're going to go.

So I think that the risk/benefit is not at all clear, but I think that we have to be very concerned about the future of risks.

DR. CARSON: I wanted to also just make some comments, and that is, a lot of things are changing. I worry very much. One of the indications, as we've heard, is the prevention of osteoporosis. So, therefore, an extended indication is T-scoreless or less negative than 2.5.

There are women now who are losing bone

because of heavy athletic activity, training for marathons, different kinds of surgery, different kinds of drugs, who are, frankly, osteopenic. It concerns me that putting them on a bisphosphonate and then having them get pregnant, even though the stop, they have continued reentry into the system of the drugs, and we really don't know what is going to happen to a fetus.

I'm sure that it's something that physicians might not -- won't treat, but I'm not at all sure that as our population changes and we see more of these patients, that some individuals won't be exposed in pregnancy, and that just not knowing what that risk is is concerning.

The other thing is, is I really have heard nothing about BMI discussed in the studies as a possible, again, either protective or additive risk for some of these injuries. I'm not sure whether BMI was in part of the exclusion factors. But as our population is becoming heavier, this might also have influence on risks and benefits.

Any other committee -- Dr. Diaz?

DR. HERNANDEZ-DIAZ: Yes. I think I'm repeating myself, but in the risk/benefit, when we look at the data from FLEX, we might or might not agree about a potential reduction in risk beyond five years. But we have to keep in mind that we are comparing -- the placebo group are patients who had been exposed for five years or so.

So we might not see a difference because they still have a protective effect, which brings us back to what I said before about assuming that stopping is going to reduce the potential risk of atypical fractures. So in the risk/benefit, we really don't have data for the risks associated with discontinuing.

DR. CARSON: Okay. So I think that, in summary, the panel has discussed various concerns about risks and benefits, and probably our consensus is that we really can't define any type of long-term risk/benefit ratio without more information.

Let's move on to question number 4. Please discuss whether restricting the duration of use or

implementing a drug holiday would be beneficial for patients requiring long-term bisphosphonate treatment for osteoporosis. Does this apply to all patients undergoing treatment for osteoporosis, or to a subset of patients, such as patients with a T-score of less than negative 2.5 and/or a prior history of fracture?

Dr. Rosen?

DR. ROSEN: I think I'll start. I think it's really important for the FDA to recognize what's happening clinically. Many patients are coming off the drug because they're concerned, and many physicians are not prescribing it now.

So I think it's really important that the FDA or our committee make a statement that, yes, this is a very important problem that we need to resolve. We obviously need more data. But safety concerns would suggest that many people probably should come off at the three-year time point.

I don't like the term "drug holiday." I think that's something we should really get away from. It makes an interpretation of going away and

not coming back and checking on the patients, and it's really -- I think that shouldn't even be in the equation.

But I do think we have an obligation as a committee to reflect what is happening in practice and what's been done in clinical trials, and that is testing the hypothesis. There may be equipoise between stopping the drug or keeping it going.

DR. CARSON: You know, along those lines, as I was thinking about this and thinking about stopping for a short time and then starting again, it also made me think, our economy is such that when folks are on these drugs, life does happen. And you sometimes lose employment and they become less available to you. And if you are able to have a five-term treatment and then miss that opportunity to go back on because you can no longer have the drug provided, then it might be something that you regret doing.

So I think the point is I think we have to be really careful about what data we do have. And it would be very nice to have 3-year data separate

from 5-year data rather than intermittent.

Dr. Burman?

DR. BURMAN: Thank you. I would like to note that the American Association of Clinical Endocrinology guidelines seem reasonable to me, and they were just published last year. And they noted that if there is mild osteoporosis, you should recommend staying on the drug for four to five years and then perhaps take a holiday. If there's severe disease with progression, then perhaps you should stay on longer; they suggest 10 years with perhaps a holiday. And I think that's good points to discuss, whether those are the right times.

But I'd also like to raise the issue that it's very arbitrary to have an arbitrary time. So doesn't it make more sense to suggest or recommend that there might be a time frame for a holiday, but also that should be in conjunction, perhaps, with biomarkers, at least some other -- clinical history, some other additional adjunctive factors to help other than an arbitrary time frame.

DR. CARSON: Dr. Suarez-Almazor?

DR. SUAREZ-ALMAZOR: Following on the discussion, I would like perhaps to have a little bit of clarification from the FDA with respect to the wording. It seems to me that "restricting the duration of use" is very strong language, as opposed to saying -- even "implementing" is a little strong, but recommending a drug holiday. And it doesn't really fit with the label that's shown underneath.

So I was wondering what is meant by restricting the duration of use.

DR. CARSON: What would you recommend?

DR. SUAREZ-ALMAZOR: Well, I like -- well, I guess it's the next discussion point. I would stay away from strong words because we don't have evidence of benefit, but that doesn't mean that there is evidence of lack of benefit.

So I think we can have a recommendation, but I don't think we have enough data to restrict anything at this point.

DR. CARSON: Dr. Johnson?

DR. JOHNSON: Yes. I would agree with the

previous speakers, that I do think that it's important to think about what physicians are already doing out in practice. And I think that patients are coming after three years or five years and saying, I hear that now I'm supposed to take a break, and so it's done.

The issue, though, really is we don't have good testing to know how long they should come off it, when they should go back on. And, in fact, the data that you have says that the markers we typically use aren't all that useful.

But I do think that that might be another potential for research, is let's do some trials looking at coming off and following those individuals with osteoporosis, or those who are in the milder category, and see if we can determine how long the holiday works, when they need to come back on. I mean, that would be an ideal study to be able to determine what a good holiday would be.

DR. CARSON: Dr. Morrato?

DR. MORRATO: Yes. I would just add that I would try to encourage us not to -- as someone said

earlier, not to use the word "drug holiday" in this because that in essence implies that you're going to come back. And based on the data that we have right now, it would suggest that even through five years, there's really no difference in fracture rate between those who stayed on drug and those that didn't.

I would agree with more or less stating guidance on what is known based on the trials, as opposed to leaving the term "holiday." Of course, if we have data that suggests that you can do that, then come back to that language.

DR. CARSON: Dr. Orza?

DR. ORZA: I'm not totally sure what my question is. But if we're talking about people --

DR. CARSON: You're answering.

DR. ORZA: If we're talking about people needing to be on this for 20 or 30 years, and then we're talking about really multiple drug holidays or multiple times of being on and coming off and going back on, and I don't see we saw any evidence at all that speaks to that.

DR. CARSON: Dr. Collins?

DR. COLLINS: I think the other language that's important to clarify, it says "requiring long-term bisphosphonate treatment for osteoporosis." Bisphosphonates aren't the only drugs for the treatment of osteoporosis, and perhaps it should be, "that require long-term treatment for osteoporosis," rather than implying that they're going to be on a bisphosphonate.

DR. CARSON: I'm sorry. I think I missed your point.

DR. COLLINS: So in other words, the language says, "requiring long-term bisphosphonate treatment for osteoporosis." Why are we locked into bisphosphonates as the only treatment for osteoporosis? There are other drugs indicated for its use. So I think that language is not the best.

DR. CARSON: Well, I think that what FDA wants to know, that in those patients who have been taking this particular drug, bisphosphonates. We're really talking about this. They'd like to know that once they are prescribed this drug,

1 should the duration be restricted?
2 DR. COLLINS: Well, I didn't -- I do not see
3 it that way at all. The way I see it, you're on a
4 bisphosphonate. You're going to take a holiday
5 from a bisphosphonate. You're going to go back on
6 a bisphosphonate. I don't think it should be
7 interpreted that way at all. I think we have to be
8 clear that there are other drugs for the treatment,
9 and if you go off that drug and you need treatment,
10 then you should consider other drugs as well.
11 DR. CARSON: Dr. Vaida?
12 DR. VAIDA: I'd just quickly like to
13 reiterate something Dr. Rosen said about like
14 sending a message that maybe you can take -- maybe
15 it's not a holiday from these drugs, but you could
16 take off.
17 But I think we have to really emphasize,
18 too, the kinetics of these drugs, and they're very
19 different, That's why even when you're talking
20 about duration -- I mean, we've even seen from some
21 of the studies that one drug, you may get a
22 decrease in markers after two or three years;

1 another one, it's six months. Even when we talked
2 about the affinity, these drugs have long, long
3 half-lives.
4 I think that's something that we do want to
5 reiterate out there, too, is that this drug hangs
6 around for several years after you get off it, just
7 as you had mentioned, too, I think is an excellent
8 point that never came up, even with the pregnancy.
9 I mean, you could stop the drug, but it doesn't
10 mean -- even with the teeth, it doesn't mean it's
11 going to go away.
12 DR. CARSON: Dr. Gut?
13 DR. GUT: I'm not sure that we are ready to
14 recommend any restriction of use without providing
15 a relevant alternative, what to do after these
16 three years. I'm also not sure that we are ready
17 to recommend this drug holiday period without
18 knowing when to start, for how long, and what is
19 the real benefit, if any, of this holiday.
20 DR. WOODS: I really like Dr. Collins'
21 suggestion. And I think, again, the FDA can
22 wordsmith this, but something to the effect of

restricting duration of use or implementing alternate treatments for a period of time would be a way to soften it and allow physicians to kind of individualize treatment to each individual's particular situation.

I think the other thing I would echo, just in some of my day-in-and-day-out interactions with physicians, is that while I do think a lot of physicians get questions from their patients about should I take this, I also see lots and lots of patients who are on autopilot and are 9, 10, 11 years into treatment and nobody has ever really asked the question, especially older patients that will not ask questions, that will go along with what the doctor said. And I think we heard a little of that from the public members today.

DR. CARSON: Dr. Johnson?

DR. JOHNSON: Yes. I just wanted to agree. We did hear people say that I think it's critical for all physicians to be aware that if we're going to put forward recommendations, that they really are clear on why; things that they should watch for

in their patients such as thigh pain, such as jaw pain. I mean, just be really clear on why this is happening and what they should be looking for for their patients.

I think it's important, because I agree. I think this is a medication that tends to be given and then forgotten. So I think the importance of all of this is that we make physicians more aware.

DR. CARSON: Okay. Let me summarize by saying that the committee felt that the calendar of use of these drugs was not really supported by any data, and that it was unclear whether any type of rest from them or discontinuation and restarting on the calendar was beneficial or detrimental; but that more data is needed, especially utilizing biomarkers and collection of other data, including alternative drugs in intervening periods, and even alternative -- or even other drugs which may be both advantageous and disadvantageous during periods of use and disuse.

Did I get that? Okay. Let's move on to the next question.

Now, this is a question that we will be voting on, and we will be using an electronic voting system for this meeting. Each voting member has three voting buttons on your microphone, "Yes," "No," and "Abstain." When it's time for a vote, please vote by pushing the button located immediately below the corresponding letter. Again, firmly push the same button three times.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen behind me. I will read the vote from the screen into the record. Then we will go around the room, and each individual who voted will state their name and vote into the record as well as the reason why they voted as they did.

So let's first discuss the question, and then we'll vote. Bisphosphonate labeling for prevention or treatment of osteoporosis currently carries the following "Important Limitation of Use":

"The safety and effectiveness of, particular drug name, for the treatment of osteoporosis are

1 based on clinical data of blank years duration.
2 The optimal duration of use has not been
3 determined. All patients on bisphosphonate therapy
4 should have the need for continued therapy
5 reevaluated on a periodic basis."
6 Do you recommend that the label should
7 further clarify the duration of use for
8 bisphosphonates? Why don't we discuss this, and
9 then we'll go around.
10 DR. ROSEN: So I have a quick question.
11 DR. CARSON: Yes?
12 DR. ROSEN: I know what's in the italics.
13 But the opening salvo is "Bisphosphonate labeling
14 for prevention or treatment of osteoporosis." So
15 I'd like a little clarification, because then in
16 the italics it says "for the treatment." The label
17 is specific for the drug for the treatment.
18 So what are we talking about here? Are we
19 talking about prevention, or treatment, or both?
20 And that has a huge bearing, I think, on our
21 discussions.
22 DR. CARSON: Dr. Kehoe?

DR. KEHOE: The Important Limitation of Use is in the indication section, and it states treatment of osteoporosis, but it's underneath all of the various osteoporosis indications that are there. But it's mainly for the treatment of osteoporosis.

DR. CARSON: I think that probably the panel wishes to express that maybe FDA needs to think about exactly these indications regarding treatment of osteoporosis, prevention of osteoporosis, treatment of osteopenia. That's the message we'll send to you today.

For now, let's discuss this as the treatment of osteoporosis, the italic version.

Dr. Madigan?

DR. MADIGAN: This is a clarification question. What would "xx" be for, say, alendronate?

DR. KEHOE: The duration of the years listed in the label are currently the clinical trial data that is listed in the label. So depending on the products, it's anywhere from one to four years.

DR. MADIGAN: So it would not include FLEX? It would not go out that far?

DR. KEHOE: FLEX is not included in the product labeling.

DR. CARSON: Dr. Vaida?

DR. VAIDA: So just as another clarification, are we talking about if we voted yes with this, that each drug would have a different duration that the FDA would come up with? Would my comment on the kinetics and how long something like -- you know, you could take one drug and --

DR. CARSON: They've asked for that recommendation.

DR. VAIDA: So they're --

DR. CARSON: If you think it should be changed, what would your recommendation be? Or if you think the duration should be there, please outline.

DR. VAIDA: Well, right now I'd have a hard time coming up with anything. But I certainly -- I'm just curious. Were you looking that there was going to be one number put on all

the drugs, like five years?

DR. KEHOE: This is current labeling right now, and it's based on what's in the product label. So the years duration listed in the label right now is 1 to 4.

Now, the way we approached this important limitation of use labeling was as a class. Each bisphosphonate has the same language except for the name of the drug and the duration of their clinical trials.

So although we've been hearing that there are a lot of issues regarding that we should potentially go back and look at these drugs as separate entities, what we were looking for here was more of, as a class, do you recommend further labeling? If you are recommending yes, that there should be further clarifications and you have certain ideas of years for one versus the other or what have you, we welcome any recommendations that you have.

DR. CARSON: Any other discussions? Dr. Morrato?

DR. MORRATO: Just a follow-up, then. What is the language for patients in the med guide, then? Does it refer to any of this at all?

DR. KEHOE: It does. We'll put up the med guide.

DR. MORRATO: And are you asking for us, then, to comment in the totality of labeling in terms of use, if we had any specific comments about the patient version as well when we vote?

DR. KEHOE: Certainly you can recommend if you do.

DR. CARSON: While were looking, let's go to Ms. Tucker's question.

MS. TUCKER: My concern is that for patient labeling, at least, that the ambiguity of having continued therapy reevaluated on a periodic basis basically means it'll never happen, and it needs to be -- from my perspective, anyway, it needs to -- whether it's yearly or whatever the committee thinks is better. But for consumer use, periodic means never.

DR. KEHOE: The current patient labeling

states, "It is not known how long drug works for the treatment and prevention of osteoporosis. You should see your doctor regularly to determine if drug is still right for you."

MS. TUCKER: Unfortunately, that still means never. Basically, for most people, it'll never come up. I really believe you need to put some sort of -- whether it's yearly -- most people, if you go for a yearly physical and you think, okay, I need to -- at this physical, I also need to talk to the doctor about the bisphosphonate that I'm on or whatever, that that's an opportunity to do it. But this particular style of language is going to go in one ear and right out the other, if the person ever even reads it at all.

DR. CARSON: Dr. Winterstein?

DR. WINTERSTEIN: I wanted to build on this. I think there is a big risk in not coming up with specific recommendations just because we don't know what the numbers are going to be, because what will happen is nothing is going to happen. And that starts with the definition of "periodic." I think

it would go further with, what would that evaluation include, and what specific parameter would I use to determine whether a patient should be continued on medication or not?

If we don't provide any kind of guidance on this with some explicit parameter, and it seems that the only one we have right now is BMD, whatever that good is, it would probably be better than doing nothing because my concern would be that there wouldn't be a whole lot of evaluation happening.

You know, I think the same thing -- if we discuss what should that time period be that we would recommend that these drugs should be taken -- obviously we don't have good data. But the flip side to this is if we don't make any recommendation, what kind of harm do we do with this, just because we don't have some explicit number?

I'll just go ahead and make a case for the five years. Looking at the drug utilization data -- that's why I asked earlier about

1 this -- there is a fraction of patients who are
2 taking these medications more than five years. In
3 fact, it's .74 percent, based on the analysis that
4 we saw here. So it doesn't really seem that there
5 is a large population that is currently using those
6 medications, and that is a user population from
7 2006, from what I understand here.
8 So it doesn't really seem that these drugs
9 are used - and, actually, in fact, half of the
10 patients discontinued therapy after half a year.
11 So it doesn't really seem that there is a very
12 large population of patients that take those
13 medications for a very long time period, which goes
14 back to what Dr. Nelson said earlier.
15 There's this issue of emerging risk. One of
16 the big reasons why we probably don't see a whole
17 lot of cases emerging is the fact that we have a
18 very, very small number of users that user these
19 medications for such a long time period. And I
20 think that's a very dangerous observation as we do
21 see that some cases are emerging.
22 So considering the fact that there's not

very many patients taking these medications for more than five years, and considering the fact that there is a safety signal that might really firm up over time as we have more patients who continue to be exposed to bisphosphonates for more than five years, it might be a good idea to take the five years for now until we have better data, and then this could be revisited, as opposed to just letting sit everything and push everything back into clinical practice and hope that people will make an informed decision, which would have to be as informed as ours today. And, obviously, we had a hard time making a decision.

DR. CARSON: Dr. Duncan?

DR. DUNCAN: We don't get a prescription that lasts forever. I mean, it's renewed every year. And it seems to me that we could be very explicit about this needs to be done annually when these drugs are renewed. I think that's the decision point.

DR. CARSON: Okay. I -- oh. Dr. Collins?

DR. COLLINS: I don't know the answer to

1 this because as a federal practitioner, it's not so
2 much an issue to me. But if you put something like
3 that in there annually and a patient isn't seen
4 annually, and then they have a fracture, is there
5 liability that is then -- does it up the liability
6 potential for the practitioner? The blame goes to
7 them that they didn't see that patient in a year?
8 I don't know.
9 DR. CARSON: Well, I think that in terms of
10 the liability, it varies from state to state, and
11 there are lots of reasons that people sue. But I
12 think that the labeling does certainly help the
13 practitioner with choices and with decisions. In
14 terms of what goes to court and how liable they
15 are, I'm not sure that we can really know that.
16 Okay -- oh. Dr. Orza?
17 DR. ORZA: One quick point. I think we're
18 rightfully concerned about what goes in the label
19 because we think that's going to have some impact
20 and influence. And I just want to remind us about
21 the number of times that it was suggested to us
22 that we think about a black box, and what we're

looking at here could not be further away from a black box. But if we really want to have some impact with this, we should be thinking in terms of something --

DR. CARSON: Okay. We're ready to vote now. So we are voting on, do you recommend that the label should further clarify the duration of use for bisphosphonates? Yes, no, or abstain. So if you think the italics should be changed, then vote yes. If you think it should not be changed, then vote no. And then we'll go around the room. And remember to hit your button three times to vote.

DR. COLLINS: We're only thinking about the italics here? Is that --

DR. CARSON: That's right. Only what's in the italics.

[Vote taken.]

DR. CARSON: There were 17 yeses, that the label should be changed, and 6 noes. So we will now go around the room to ask you for your answer and your reasoning.

Dr. Gut? Oh, you're not voting. Sorry.

Dr. Miller?

DR. MILLER: Yes. I voted yes. And I do think we could probably expand and maybe make a difference in terms of what physicians read. And I guess in terms of -- based on clinical data of "xx" years duration, whether that should be changed, I don't know. It sounds like that's already appropriately, maybe, labeled for each drug.

But I think maybe the optimal duration of use has not been determined. And some patients may benefit from continued therapy, and some may not benefit from continued -- or may develop risks. "And this is being further explored," could be added.

DR. CARSON: Dr. Johnson?

DR. JOHNSON: Yes. I voted yes. I heard what Ms. Tucker said, and I really did think that perhaps this should be edited saying, "continued therapy reevaluated on a one- to two-year basis," something that defines a period of time which we should reevaluate, so this is discussed with patients, so as new data and information comes

forth, the physicians discuss this issue with their patients.

DR. CARSON: Dr. Cooper?

DR. COOPER: I actually voted no. And I was really responding to the question about whether the label should clarify the duration of use for the medications. And I feel like that given the limited data we have, the language that's currently in there captures what we know about that.

I do agree with my colleagues that if there are changes to be made to this section, adding information about talking with your healthcare provider or talking with a patient about the need for the continued therapy as well as the potential risks, because the balance, the risk/benefit balance, may change in those later years after they've been on the medication for a while.

DR. CARSON: Dr. Nelson?

DR. NELSON: Yes. Lewis Nelson. I voted yes. I think I was concerned that it doesn't highlight enough currently about some of the risks that we're facing. I did originally think that

this should probably be moved from something as simple as an important limitation to, if not a boxed warning, a warning, perhaps, something a little bit more dramatic that should say two things.

One, it should say that efficacy may fall off -- in fact, be very clear that efficacy may fall off after a period of time, perhaps five years, and that risk is -- serious concerns have been raised about risk, and those need to be continually reevaluated as well.

So we have to suggest that efficacy is not necessarily permanent, and that risk is a moving target. And I just think that, in general, the strength of this has to be beefed up a little bit on both ends.

DR. CARSON: Dr. Erstad?

DR. ERSTAD: I voted yes, for many of the same reasons, and also for some of the reasons expressed earlier, that I'm concerned that just "reevaluated on a periodic basis" sounds so generic, it sounds like it applies to virtually any

drug out there.

Even though it wasn't part of the question, but I think as important -- it was a point that was brought up earlier in terms of the information that does go to the patient, because if you look at that information, it lists some of these serious adverse effects, but it's more in a retrospective manner, as though once these occur. Well, then, obviously, if it hasn't been noted already, you should be reporting them. And it really to me seems that it needs to be in a more proactive manner, that this should be the basis for your discussion, then, at this period of time you really should be having this discussion.

So, again, addressing it more proactively and reactively and making sure it's also in that patient information since I'm counting on them at least as much as a healthcare professional to pick this up.

DR. CARSON: Dr. Suarez-Almazor?

DR. SUAREZ-ALMAZOR: Yes. I voted yes because I think there's not sufficient evidence to

continue the therapy with the drug on the basis of what has been presented today. And there are some signals of infrequent and rare adverse events, but that can be very damaging and deleterious.

As far as changing the labeling, I would probably add something, after, "The optimal duration of use has not been determined," something like, "and it isn't clear whether patients continue to benefit after three to five years of therapy."

At the end, I understand that it's important to evaluate the drug every year, so perhaps leave the "reevaluated on a periodic basis," but add something such as, "After five years, careful consideration should be given to potential continuing benefits versus risks associated with long-term use of these drugs."

DR. CARSON: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: I voted yes because I believe that there might be a change that we can do that further clarify what we mean. And once we have in the first sentence the number of years for which we have data, I will replace the second

sentence by something like, "The safety and effectiveness of the drug for longer duration of use has not been determined."

DR. CARSON: Dr. Vaida?

DR. VAIDA: Allen Vaida, and I voted no. And that was actually addressing the clarification of the duration. And I really felt that there wasn't enough evidence or information on what that duration should be, that the drug's very different. Hopefully, from the duration standpoint, too, as was mentioned, it's less than 1 percent taking it over five years, and hopefully that is something that's coming across now.

DR. CARSON: Dr. Madigan?

DR. MADIGAN: I voted yes, for basically the reasons that have been articulated. Just one extra comment on the first sentence, and it just -- the safety and effectiveness of, let's say, Fosamax for the treatment of osteoporosis are based on clinical data of five years duration. I hope that would not be interpreted to mean that the drug is definitively known to be safe and effective when

taken for five years. The wording is just in some sense very strong.

DR. CARSON: We're going to go to this end of the table. Dr. Kittelson?

DR. KITTELSON: Thank you very much; airplanes. I voted no, partly for reasons of lack of information on exactly what these risks are, exactly good data on how we would advise in terms of duration.

The second element is I'm worried about the same thing that Dr. Rosen brought up, and that's the exodus from bisphosphonates even though they've been shown to have quite a dramatic reduction in fractures in the registration trials and in other kinds of data. So I don't want to send a false warning. I don't want to cry wolf on this. Thank you.

DR. CARSON: Dr. Hoeger?

DR. HOEGER: I voted yes, echoing some of the previous comments. I agree that "The optimal duration of use has not been determined" is an inadequate statement, although it is reflected in

the literature. But things to consider would be the fact that "We have really no good data on long-term use" should be included in that statement, and also agree that we should add a specific evaluation, not periodic, but one to two years.

DR. CARSON: Dr. Clarke?

DR. CLARKE: I voted no, for the same reasons expressed. I think it's premature, based on the data that we've heard, to put a specific restriction on the dose duration.

The other issue is that, practically speaking, I think physicians are forced every year, every time they renew prescriptions, to reconsider these same issues. To some degree they're not considering all the issues because they're not aware of some of the things we've heard today. But I think, practically speaking, every time I see a patient, I'm looking at every drug they're on and I'm saying, is this drug still needed? That specifically applies to bisphosphonates, but to every other drug as well. And I think, ethically, that's what physicians will do in practice.

1 DR. CARSON: Dr. Orza?
2 DR. ORZA: I voted yes, for many of the
3 reasons that have already been expressed. I think
4 what I have in mind mainly is that we're talking
5 about the label as being the vehicle through which
6 we communicate the importance of this to both the
7 clinical community and the patient community.
8 I think, one, that the wording of this needs
9 to be strengthened and elevated somehow from being
10 simply important limitations of use, and that we
11 need to think about other things, like the large
12 group of people who've already been on these for
13 5 or more years and what we say to them. And we
14 have to deal with this prevention of osteoporosis
15 issue. If we're not even comfortable saying that
16 the risk/benefit calculation looks good for these
17 very high-risk people, what does that mean we're
18 saying about so-called prevention of osteoporosis?
19 DR. CARSON: I voted no because I'm
20 convinced these drugs are efficacious in the
21 treatment of osteoporosis, patients benefit, and
22 that until we know more about long-term therapy, we

1 should keep the wording with what we know.
2 MS. TUCKER: I voted yes. I think it needs
3 to be more strongly worded, but I also think that
4 instead of "periodic basis," it should be
5 "annually." It gives a person an opportunity to
6 talk their doctor. That way, though, possibly if
7 there's something going on, they can express that
8 at the time. And I think this is really important.
9 DR. CARSON: Dr. Woods?
10 MS. TUCKER: I'm sorry. I'm Elizabeth
11 Tucker.
12 DR. WOODS: I voted yes. I really have
13 nothing to add other than, again, I would highlight
14 what Dr. Collins said. If we could maybe weave
15 into the wording that it's not a holiday from the
16 treatment of your osteoporosis; it's maybe just
17 different treatment for a while.
18 DR. CARSON: Dr. Morrato?
19 DR. MORRATO: Yes. I voted yes. I'd like
20 to see the labeling changed. And I'd like to first
21 commend the FDA for getting some initial language
22 already in place on this. It's nice to react. It

sounds like many colleagues are talking about tweaking language as opposed to creating it from scratch, so I think that's good.

So when I considered what would I change, I was weighing two options. One is the risk of over-alarming if we over-label, and I didn't feel that the evidence was there to mandate a fixed duration of use, and that I was concerned about the message that would send to patients in scaring them away from a drug that has a lot of benefit in terms of mortality and fracture rates.

On the other hand, I was concerned about the risk of under-warning. So when I look at the specific language right now -- I think Dr. Madigan was referring to some of this, too -- it reflects just what's in the clinical trial data, which is three to five years, or up to four.

The message almost comes across, at least to me, that, gee, we don't have longer term safety data at all; we just have what we have in the trial data. And I think after hearing the FLEX analyses, et cetera, that you all presented, I would like to

see that kind of data incorporated in here because there is data that would suggest that discontinuation rates -- you may see a maintenance of benefit, et cetera.

So we do have longer term data that I think should be somehow incorporated. And I would agree with others, when they're talking about specificity with regard to periodic updating, and that if there is data, we heard some that's talking about risk factors for those who might be at greater risk for fractures, as we heard from like Dr. Bauer. After a full analysis of these data, that could be incorporated as well as guidance. I think it gives greater specificity.

Then the last thing I would say is I would vote in favor of more class-type language for these sorts of guidance on the long-term use as opposed to everything being drug-specific because, obviously, we have some drugs that have the long-term data and others don't. And that might leave the message that if you're adding in the long-term safety data on some and not the others, it means

the others might be safer than one or the other. So I think you want to avoid that.

DR. CARSON: Dr. Winterstein?

DR. WINTERSTEIN: Almut Winterstein. I voted yes for the reasons I expressed earlier. I agree that a recommendation for a periodic evaluation should be explicit, made explicit, not only in terms of the time sequence but also what specific parameters should be used to identify a patient who might warrant extended therapy.

In terms of adding information about risk and benefit, I like the way that Dr. Nelson has phrased this earlier, so I will refrain from repeating that again.

DR. CARSON: Dr. Burman?

DR. BURMAN: Thank you. I voted yes. I thought the statement was too general, and I do have some recommendations that shouldn't be mandated, but recommendations.

The data are strongest for a benefit compared to a risk for zero to five years of bisphosphonate therapy. The use should be

individualized, especially for patients taking the agent between 5 to 10 years, where the risk/benefit ratio is not clear.

Periodic monitoring of patients in discussion with their healthcare provider should be performed. And data for the use of the drug for more than 10 years is not clear; its safety and efficacy isn't clear.

DR. CARSON: Dr. Rosen?

DR. ROSEN: I'm Cliff Rosen, and I agree with Dr. Burman, actually. He phrased it very well. Two things that I want to point out.

One, I would not put any limitation on such as five years for continued therapy because I think we would handcuff a whole bunch of osteoporotic doctors who can continue to take care of patients on bisphosphonates and show fracture risk reductions. So I think adding some limit would be over the top, and I'm really against that.

I also think it's very important to reconsider what we're doing when we're talking about osteopenia and prevention with the use of

these drugs. So I think that has to be considered within the entire framework.

Otherwise, I think the wording that Dr. Burman had given us is quite appropriate.

DR. CARSON: Dr. Collins?

DR. COLLINS: I'm Michael Collins. I voted yes, they should be changed, and all the reasons for which I said that have already previously been stated. In general, I think the current language isn't strong enough. I think more specifics along the lines of what Dr. Burman mentioned should be included. And I echo Dr. Rosen's concerns about what really reflects overuse of the drugs, I think.

DR. CARSON: Dr. Ruppe?

DR. RUPPE: I'm Mary Ruppe, and I voted yes. And I agree with what the last three people said as well. I think, really, you have to add some specifics to the word "periodic," but also bring into the notion in this statement that an individualized risk/benefit assessment for continued therapy needs to be undertaken.

DR. CARSON: Dr. Duncan?

DR. DUNCAN: I'm Bill Duncan, and I voted no because I don't believe we have enough data to limit the duration of use, which was the question that was put before us to vote upon.

Now, I do agree that the italics could be strengthened and should be strengthened to remind the providers to address the risk/benefits, especially after five years of treatment.

DR. CARSON: Thank you.

Now, for the final question, we have only about five minutes. So I'm going to expedite it a little bit.

Please discuss for which outcomes further evidence should be obtained, how best that might be accomplished, and in what priority order they should be investigated: atypical subtrochanteric and femur fractures; osteonecrosis of the jaw; esophageal cancer; osteoporotic fracture reduction efficacy with long-term, greater than three to five years, continuous bisphosphonate use; the effect of a drug holiday on bisphosphonate safety and effectiveness.

Now, I think that the panel has already said in various forms that they feel further evidence is needed for all of these disorders.

Is that correct?

[Members nod affirmatively.]

DR. CARSON: Okay. So we can expedite that. And why don't we give -- Dr. Collins, let me put you on the spot, and why don't you give us a rough priority order of these, and then we'll change it, unless anybody else feels strongly.

DR. COLLINS: Okay. Well, certainly one of the highest, if not the highest, is the atypical fractures; and then possibly, two, osteoporosis fracture reduction efficacy; then osteonecrosis of the jaw; then drug holiday; then cancer, esophageal cancer.

Is that all of them?

DR. CARSON: Okay. Now, let's have the other panel members discuss that order. Dr. Morrato?

DR. MORRATO: I might --

DR. CARSON: Let me repeat the order.

Atypical fractures; osteoporotic fracture reduction; osteonecrosis of the jaw; drug holiday; and esophageal cancer -- 1, 3, 5, 2, 4.

Dr. Morrato?

DR. MORRATO: Yes. Rather than rank ordering, I would put the study of the effect of drug holiday or discontinuation higher on the list, mainly because if folks are following what might be changes to the labeling, we're going to have a huge natural experiment occurring. And we should understand what's happening in the clinical population.

DR. CARSON: And how might that be accomplished?

DR. MORRATO: Well, I mean, this would be an ideal use of the Sentinel Initiative, if you're actually able to look at large populations of people. I think the challenge will be defining what is a discontinuation, and then do you have enough long-term follow-up within those data sets.

But I think you could at least start with what's happening in year 1, year 2, and at least be

1 describing it. I think we should be kind of doing
2 an active surveillance around this; and it may not
3 be definitively sized and all that, but we should
4 be actively engaged.
5 DR. CARSON: Dr. Nelson?
6 DR. NELSON: I think we have to put the risk
7 and benefit at the top. And, clearly, the big
8 efficacy issue is osteoporotic fracture reduction,
9 I think, and I actually think that should be the
10 top one.
11 I think the big risk that we don't know is
12 the atypical fractures. You know, osteonecrosis
13 and esophageal cancer are obviously important if
14 you have them, but they seem like they're very
15 uncommon, by all other accounts that we've seen
16 today. So I'd probably put those two towards the
17 bottom. And certainly esophageal cancer, I think,
18 would go at the bottom. And I think that the drug
19 holiday or osteonecrosis kind of will fight for
20 third and fourth position.
21 So I would have osteoporotic, atypical,
22 probably drug holiday, then osteonecrosis, then

1 esophageal cancer. That's not my typical way of
2 doing things, but it just seems like understanding
3 fracture reduction would be very important to
4 understanding everything else.
5 DR. CARSON: Okay. Dr. Suarez-Almazor?
6 DR. SUAREZ-ALMAZOR: Yes. I agree with that
7 because if there's no fracture reduction efficacy,
8 there's not even any point in talking about
9 anything else. We need to know that's efficacious,
10 which it might be. We don't know.
11 DR. CARSON: Yes, Dr. Hoeger?
12 DR. HOEGER: I heard just
13 mentioned -- someone had brought up earlier a delay
14 of wound healing, and we had talked about that as
15 potentially being an important adverse outcome that
16 would certainly have a cost-effective issue for
17 this.
18 DR. CARSON: Dr. Rosen?
19 DR. ROSEN: Yes. I think the fundamental
20 issue remains safety, and the atypical fractures
21 are number 1, 2, and 3 in my mind. We have to
22 understand mechanism, and we have to understand the

prevalence, and we have to understand who we can identify at risk.

That's what everybody talked about. Every consumer came here and talked about subtrochanteric fractures. That's what's raised the issue with the FDA. And I think that should be our primary responsibility. And I think it's both biological mechanism, because we don't know who these people are; we don't understand.

The bone biopsies and the histomorphometry are perfect. There's not a mineralization defect. That's not the issue. There's something biologically different, and there's something that puts these people at risk. And we have to find out what that is.

So my priority is still with subtrochanteric fractures as number 1.

DR. CARSON: And the final comment is from Dr. Woods.

DR. WOODS: I would just echo the wound healing comment. And I think someone earlier suggested that maybe working closely with the

dentists and the oral surgeons might be a route that we could use to accumulate some data quickly.

Adjournment

DR. CARSON: Okay. There's no real consensus as to the order; however, I think we all agreed that esophageal cancer should be final. And there's some question as to -- parts of the committee feel that atypical fractures and ONJ should be above the last two, and the other parts of the committee feel that the drug calendar and efficacy should be above that.

I'm not sure -- let me ask FDA if -- we are out of time, but if we can answer in maybe an extended five minutes any other questions that you would like us to discuss in this final question.

Is that okay? You're all right? Okay.

Panel, thank you so much. You've been terrific, fun to work with. Lots of new friends met at lunch. And those of you who are interested in FDA history, it's quite a fascinating history. The oral contraceptive was the first drug that had a patient education insert. And FDA has a long

history that was largely a grassroots initiative because the public wanted more information about harmful effects of drugs and drug effects.

Today's meeting, I think, really is so much not only in the spirit but the history of the FDA. Thank you all so much again.

(Whereupon, at 4:32 p.m., the meeting was concluded.)