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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

BONE, REPRODUCTIVE, AND UROLOGIC DRUGS
ADVISORY COMMITTEE (BRUDAC) MEETING

Wednesday, January 16, 2019

8:15 a.m. to 4:00 p.m.

FDA White Oak Campus
Building 31, The Great Room
10903 New Hampshire Avenue
Silver Spring, Maryland

1 **Meeting Roster**

2 **DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Kalyani Bhatt, BS, MS**

4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

7
8 **BONE, REPRODUCTIVE, AND UROLOGIC DRUGS ADVISORY**

9 **COMMITTEE MEMBERS (Voting)**

10 **Douglas C. Bauer, MD**

11 Professor of Medicine and Epidemiology &

12 Biostatistics

13 University of California, San Francisco

14 San Francisco, California

15
16 **Roger T. Dmochowski, MD**

17 Professor of Urology

18 Director, Pelvic Medicine and Reconstruction

19 Fellowship

20 Department of Urology

21 Vanderbilt University Hospital

22 Nashville, Tennessee

1 **Beatrice J. Edwards, MD, MPH, FACP** (*via phone*)

2 Associate Professor

3 Department of General Internal Medicine

4 Division of Internal Medicine

5 University of Texas MD Anderson Cancer Center

6 Houston, Texas

7

8 **Vivian Lewis, MD**

9 (*Chairperson*)

10 Vice Provost for Faculty Development & Diversity

11 Professor, Obstetrics and Gynecology

12 University of Rochester

13 Rochester, New York

14

15 **Pamela Shaw, PhD**

16 Associate Professor

17 Department of Biostatistics and Epidemiology

18 University of Pennsylvania School of Medicine

19 Philadelphia, Pennsylvania

20

21

22

1 **BONE, REPRODUCTIVE, AND UROLOGIC DRUGS ADVISORY**

2 **COMMITTEE MEMBER (Non-Voting)**

3 **Gerard G. Nahum, MD, FACOG**

4 *(Industry Representative)*

5 Vice President of Global Development, General

6 Medicine

7 Women's Healthcare, Long-Acting Contraception,

8 Medical Devices, and Special Projects

9 Bayer HealthCare Pharmaceuticals, Inc.

10 Parsippany, New Jersey

11
12 **TEMPORARY MEMBERS (Voting)**

13 **Robert A. Adler, MD**

14 Chief, Endocrinology and Metabolism

15 McGuire Veterans Affairs Medical Center

16 Professor of Internal Medicine and of Epidemiology

17 Virginia Commonwealth University School of Medicine

18 Richmond, Virginia

19

20

21

22

1 **Michael Blaha, MD, MPH**

2 Assistant Professor of Medicine and Epidemiology

3 Director of Clinical Research

4 Johns Hopkins Ciccarone Center for the

5 Prevention of Heart Disease

6 Baltimore, Maryland

7

8 **Glenn D. Braunstein, MD**

9 Professor of Medicine

10 Cedars-Sinai Medical Center

11 Professor of Medicine Emeritus

12 The David Geffen School of Medicine at UCLA

13 Los Angeles, California

14

15 **Kenneth D. Burman, MD**

16 Chief, Endocrine Section

17 Medstar Washington Hospital Center

18 Professor, Department of Medicine

19 Georgetown University

20 Washington, District of Columbia

21

22

1 **Natalie Compagni-Portis**

2 *(Patient Representative)*

3 Oakland, California

4

5 **Tobias Gerhard, PhD, RPh**

6 Associate Professor of Pharmacoepidemiology

7 Ernest Mario School of Pharmacy, and

8 Institute for Health, Health Care Policy and Aging

9 Research

10 Rutgers University

11 New Brunswick, New Jersey

12

13 **Sundeep Khosla, MD**

14 Professor of Medicine and Physiology

15 Mayo Clinic

16 Rochester, Minnesota

17

18

19

20

21

22

1 **Frederick G. Kushner, MD, FACC, FAHA, FSCAI, FACP**

2 West Jefferson Heart Clinic of Louisiana

3 Clinical Professor of Medicine

4 Tulane University School of Medicine

5 Clinical Professor of Medicine

6 LSU Health Science Center

7 Adjunct Professor of Medicine New York

8 University School of Medicine

9 New Orleans, Louisiana

10

11 **A. Michael Lincoff, MD**

12 Director, Cleveland Clinic Coordinating Center
13 for Clinical Research (C5Research)

14 Vice Chairman, Department of Cardiovascular
15 Medicine and Lerner Research Institute

16 Professor of Medicine

17 Cleveland, Ohio

18

19

20

21

22

1 **Michele Orza, ScD**

2 *(Acting Consumer Representative)*

3 Chief of Staff

4 Patient-Centered Outcomes Research Institute

5 (PCORI)

6 Washington, District of Columbia

7

8 **Clifford J. Rosen, MD**

9 Senior Scientist

10 Director, Center for Clinical & Translational

11 Research

12 Main Medical Center Research Institute

13 Scarborough, Maine

14

15 **Maria E. Suarez-Almazor, MD, PhD**

16 Barnts Family Distinguished Professor

17 Head, Section of Rheumatology and Clinical

18 Immunology

19 University of Texas MD Anderson Cancer Center

20 Houston, Texas

21

22

1 **Thomas J. Wang, MD**

2 Director, Division of Cardiovascular Medicine
3 Physician-in-Chief, Vanderbilt Heart and
4 Vascular Institute
5 Professor of Medicine
6 Gottlieb C. Friesinger II Chair in Cardiovascular
7 Medicine
8 Nashville, Tennessee

9

10 **Thomas J. Weber, MD**

11 Associate Professor, Endocrinology,
12 Metabolism and Nutrition
13 Duke University Medical Center
14 Durham, North Carolina

15

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

17 **Hylton V. Joffe, MD, MMSc**

18 Director
19 Division of Bone, Reproductive and
20 Urologic Products (DBRUP)
21 Office of Drug Evaluation III (ODE III)
22 Office of New Drugs (OND), CDER, FDA

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Tae Hyun Jung, PhD

Statistical Reviewer
Division of Biometrics VII
Office of Biostatistics
Office of Translational Sciences, CDER, FDA

Theresa Kehoe, MD

Cross Discipline Team Leader
DBRUP, ODE III, OND, CDER, FDA

Wei Liu, PhD, MSc

Reviewer
Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
CDER, FDA

Jacqueline Karp, MD

Clinical Reviewer
DBRUP, ODE III, OND, CDER, FDA

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1 P R O C E E D I N G S

2 (8:15 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

5 DR. LEWIS: Good morning. I'd like to call
6 the meeting to order, please. I'd like to first
7 remind everyone to please silence your cell phones,
8 smartphones, or other devices if you haven't
9 already done so. We'll start the meeting by
10 introducing the members of the panel and the FDA
11 group to go around the table and please introduce
12 themselves for the record.

13 Could we start with Dr. Joffe?

14 DR. JOFFE: Good morning, everybody. I'm
15 Hylton Joffe. I'm the director of FDA's Division
16 of Bone, Reproductive, and Urologic Products.

17 DR. KEHOE: Therese Kehoe, clinical team
18 leader.

19 DR. KARP: Jacqueline Karp, clinical
20 reviewer.

21 DR. JUNG: Tae Hyun Jung, statistical
22 reviewer.

1 DR. SUAREZ-ALMAZOR: Good morning, Maria
2 Suarez-Almazor. I'm a rheumatologist and clinical
3 epidemiologist at the University of Texas
4 MD Anderson Cancer Center.

5 DR. LIU: Good morning. I'm Wei Liu,
6 Division of Epidemiology II.

7 DR. LINCOFF: Michael Lincoff,
8 interventional cardiologist from the Cleveland
9 Clinic.

10 DR. BLAHA: Hi. Mike Blaha, Johns Hopkins
11 Ciccarone Center for the Prevention of Heart
12 Disease.

13 DR. KUSHNER: Fred Kushner, clinical
14 cardiologist, Tulane, and adjunct at NYU.

15 DR. WANG: Thomas Wang, chief of cardiology,
16 Vanderbilt University.

17 DR. SHAW: Pamela Shaw. I'm a statistical
18 reviewer from the University of Pennsylvania.

19 MS. BHATT: Good morning. I'm Kalyani
20 Bhatt. I'm with the Division of Advisory
21 Consultants Management.

22 DR. LEWIS: Vivian Lewis, University of

1 Rochester.

2 DR. BAUER: Good morning. Doug Bauer. I'm
3 a general internist and epidemiologist from the
4 University of California San Francisco.

5 DR. DMOCHOWSKI: Roger Dmochowski. I'm a
6 urologist at Vanderbilt Medical Center.

7 MS. COMPAGNI-PORTIS: Natalie Compagni-
8 Portis, patient representative

9 DR. ORZA: Michelle Orza with the
10 Patient-Centered Outcomes Research Institute. I'm
11 the acting consumer representative today.

12 DR. ADLER: I'm Bob Adler, endocrinologist
13 at the VA hospital in Richmond and Virginia
14 Commonwealth University.

15 DR. BRAUNSTEIN: Good morning. I'm Glenn
16 Braunstein. I'm an endocrinologist, Cedars-Sinai
17 Medical Center and UCLA in Los Angeles.

18 DR. KHOSLA: Sundeep Khosla. I'm an
19 endocrinologist at the Mayo Clinic in Rochester,
20 Minnesota.

21 DR. BURMAN: Ken Burman, chief of
22 endocrinology at MedStar Washington Hospital Center

1 and a professor at Georgetown.

2 DR. ROSEN: Cliff Rosen, endocrinologist,
3 Maine Medical Center.

4 DR. WEBER: Tom Weber, endocrinologist at
5 Duke University in Durham, North Carolina.

6 DR. GERHARD: Tobias Gerhard,
7 pharmacoepidemiologist at Rutgers University.

8 DR. NAHUM: Good morning. Gerard Nahum.
9 I'm with Bayer Pharmaceuticals, vice-president of
10 research and development.

11 DR. LEWIS: We have one panel member joining
12 us by phone.

13 DR. EDWARDS: Yes. This is Beatrice
14 Edwards. I'm at the University of Texas Dell
15 Medical School and the Central Texas VA in Temple.

16 DR. LEWIS: Thank you, everyone.
17 Kalyani?

18 **Conflict of Interest Statement**

19 MS. BHATT: Good morning.

20 The Food and Drug Administration is
21 convening today's meeting of the Bone,
22 Reproductive, and Urologic Drugs Advisory Committee

1 under the authority of the Federal Advisory
2 Committee Act, FACA, of 1972. With the exception
3 of the industry representative, all members and
4 temporary members of the committee are special
5 government employees or regular federal employees
6 from other agencies and are subject to federal
7 conflict of interest laws and regulations.

8 The following information on the status of
9 this committee's compliance with federal ethics and
10 conflict of interest laws, covered by but not
11 limited to those found at 18 U.S.C. Section 208, is
12 being provided to participants in today's meeting
13 and to the public.

14 FDA has determined that members and
15 temporary voting members of this committee are in
16 compliance with the federal ethics and conflict of
17 interest laws.

18 Under 18 U.S.C. Section 208, Congress has
19 authorized FDA to grant waivers to special
20 government employees and regular federal employees
21 who have potential financial conflicts when it is
22 determined that the agency's need for a special

1 government employee's services outweighs his or her
2 potential financial conflict of interest, or when
3 the interest of a regular federal employee is not
4 so substantial as to be deemed likely to affect the
5 integrity of the services which the government may
6 expect from the employee.

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

18 Today's agenda involves biologics license
19 application BLA 761062, romosozumab injection
20 submitted by Amgen for the proposed indication of
21 treatment of osteoporosis in postmenopausal women
22 at high risk for fracture, defined as a history of

1 osteoporotic fracture or multiple risk factors for
2 fracture, or patients who have failed or are
3 intolerant of other available osteoporosis therapy.

4 This is a particular matters meeting during
5 which specific matters related to Amgen's BLA will
6 be discussed. Based on the agenda for today's
7 meeting and all financial interests reported by the
8 committee members and temporary voting members, no
9 conflict of interest waivers have been issued in
10 connection with this meeting.

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

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

1 We would like to remind members and
2 temporary voting members that if the discussions
3 involve any other products or firms not already on
4 the agenda for which an FDA participant has a
5 personal or imputed financial interest, the
6 participants need to exclude themselves from such
7 involvement, and their exclusion will be noted for
8 the record.

9 FDA encourages all participants to advise
10 the committee of any financial relationships that
11 they may have with the firm at issue. Thank you.

12 DR. LEWIS: One more little bit before we
13 introduce the FDA to begin their opening remarks.

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

1 productive meeting.

2 In the spirit of the Federal Advisory
3 Committee Act and the Government in the Sunshine
4 Act, we do ask that committee members take care
5 that their conversations about the topic at hand
6 take place only in the open forum of the meeting.

7 We are aware that members of the media are
8 anxious to speak with FDA about these proceedings,
9 however, FDA will refrain from discussing the
10 details of this meeting with the media until its
11 conclusion. And also, the committee is reminded to
12 please refrain from discussing the meeting topic
13 during breaks or during lunch. Thank you.

14 I think with that, we're ready to go ahead
15 and invite the FDA to provide us with some opening
16 remarks.

17 **FDA Opening Remarks - Hylton Joffe**

18 DR. JOFFE: Good morning, everybody. My
19 name's Hylton Joffe. I'm the director of FDA's
20 Division of Bone, Reproductive, and Urologic
21 Products. I'd like to welcome you all here today.
22 I think we got lucky with the weather. One or two

1 days one way or the other way, I think we might
2 have had to reschedule.

3 What I'm going to do over the next few
4 minutes is basically lay some of the groundwork for
5 why we're here today. We're talking about a
6 marketing application for romosozumab for the
7 treatment of postmenopausal osteoporosis.

8 Romosozumab is a monoclonal antibody that
9 inhibits sclerostin, and if approved, it would be
10 the only product on the market that works by this
11 mechanism of action. And as you'll hear in more
12 detail over presentations, over the course of the
13 day, by inhibiting sclerostin, romosozumab
14 stimulates bone formation, and to a lesser extent,
15 inhibits bone resorption.

16 Now, currently approved osteoporosis
17 therapies have one of two indications. There's a
18 general treatment of postmenopausal osteoporosis
19 indication, and then we have a narrower indication,
20 which is the treatment of postmenopausal
21 osteoporosis in women at high risk for fracture.
22 And this narrow indication, we reserve for those

1 products that have serious side effects to ensure
2 that the indicated population has benefits that
3 outweigh the risks with those therapies.

4 Amgen is seeking the broad treatment of
5 postmenopausal osteoporosis indication. The
6 applicant is proposing a 120-milligram once-monthly
7 dose that's given as back-to-back 60-milligram
8 injections, and it's administered by the healthcare
9 provider. The proposed treatment duration is
10 1 year, and then patients switch to antiresorptive
11 therapy.

12 Today, we're going to be focusing on two
13 phase 3 fracture outcome trials conducted in
14 postmenopausal women with osteoporosis. The first
15 trial, I'm going to refer to as trial 337, which
16 enrolled over 7,000 women and randomized them to
17 1 year of double-blind romosozumab or placebo, and
18 then after that year, all women received open-label
19 denosumab, which is a rank ligand inhibitor that's
20 approved for the treatment of postmenopausal
21 osteoporosis.

22 The other trial is trial 142. This trial

1 enrolled about 4,000 women. These women were at
2 higher risk for fracture than those enrolled in the
3 placebo-controlled trial. And this trial
4 randomized women to 1 year of double-blind
5 romosozumab or alendronate, which is an approved
6 bisphosphonate that's commonly used for treating
7 postmenopausal osteoporosis. After that year, all
8 women received at least 1 year of open-label
9 alendronate.

10 The next two slides, I'm just going to give
11 an overview of some of the efficacy findings.
12 You'll be hearing these in more detail over the
13 course of the day. And I'm going to focus on the
14 positive fracture outcomes that were included in
15 the prespecified hierarchical testing strategy in
16 both trials.

17 For trial 337, this is the placebo-
18 controlled trial, 1 year of treatment with
19 romosozumab significantly reduced the risk of
20 morphometric vertebral fractures over that year
21 compared to placebo. This was statistically
22 significant. In the relative risk reduction, you

1 can see there is 73 percent.

2 Similarly, 1 year of romosozumab and then
3 1 year of denosumab significantly reduced the risk
4 of morphometric vertebral fractures through
5 month 24 compared to placebo, followed by denosumab
6 with a relative risk reduction of 75 percent.

7 These two were the co-primary efficacy
8 endpoints in the trial, and a morphometric
9 vertebral fracture is one that's detected on
10 imaging that may or may not be symptomatic.

11 Now, the next endpoint that the company
12 tested was clinical fracture at 12 months, and this
13 was a composite of non-vertebral fractures and
14 symptomatic vertebral fractures. And again,
15 romosozumab significantly reduced the risk of
16 clinical fracture through month 12 compared to
17 placebo with a 36 percent relative risk reduction.

18 Now, it's worth noting in this trial that
19 the next endpoint to be tested was nonvertebral
20 fracture by itself, and that endpoint was not
21 significantly improved with romosozumab compared to
22 placebo, so all further hierarchical testing

1 stopped.

2 When we look at trial 142, this is the
3 alendronate-controlled trial, the endpoints were a
4 little different to the ones in the placebo-
5 controlled trial. Again, the first two rows are
6 the co-primary efficacy endpoints. You can see
7 that 1 year of romosozumab followed by 1 year of
8 alendronate reduced the risk of morphometric
9 vertebral fractures through month 24 compared to
10 alendronate alone, with a relative risk reduction
11 of 50 percent.

12 Clinical fracture, defined the same way as
13 in the previous trial, was also significantly
14 reduced with romosozumab and then alendronate
15 compared to alendronate alone. And in this trial,
16 nonvertebral fracture, then, was also significantly
17 reduced by 20 percent with romosozumab, then
18 alendronate, compared to alendronate alone.

19 Now, it's important to note that neither
20 trials were powered on hip fractures or included
21 hip fractures in the prespecified endpoints that
22 won, but of course, hip fracture is an endpoint

1 that we're interested in osteoporosis trials
2 because of the associated morbidity and mortality,
3 so we'll cover that endpoint in more detail over
4 the presentations today.

5 What gets us here today is that in the
6 alendronate controlled fracture outcome trial,
7 there is a finding of cardiovascular harm with
8 romosozumab that's not seen in the placebo-
9 controlled trial.

10 The company built into their phase 3
11 protocols adjudication for cardiovascular serious
12 adverse events. This was carried out by DCRI, or
13 the Duke Clinical Research Institute, and then
14 after this finding of harm emerged in one of the
15 trials, the company undertook a second adjudication
16 that included non-serious cardiovascular events,
17 and that was done by Harvard's TIMI group.

18 Our FDA presentations today are going to
19 focus on the DCRI-adjudicated analyses because this
20 is what was built into the protocol. I will note
21 that the results with TIMI are very similar to
22 those of the DCRI. Then we're also going to focus

1 on MACE, or major adverse cardiac events, which is
2 a composite of cardiovascular death, nonfatal
3 myocardial infarction, and nonfatal stroke, which
4 is a typical way of looking at cardiovascular risk.

5 This slide summarizes these cardiovascular
6 findings over the 1-year double-blind treatment
7 period. On the left, we have the placebo-
8 controlled trial 337 and on the right, the
9 alendronate-controlled trial, 142. As you can see,
10 there's no clear signal for MACE in the placebo-
11 controlled trial with 1 year of therapy, with a
12 hazard ratio of 1.03 and a 95 percent confidence
13 interval from 0.62 to 1.72.

14 In contrast, in the alendronate-controlled
15 trial, the hazard ratio for MACE with romosozumab
16 compared to alendronate was 1.87 with a lower bound
17 of the 95 percent confidence interval of 1.11 and
18 an upper bound of 3.14. You can see the components
19 for MACE have a hazard ratio that ranges from 1.42
20 from cardiovascular death up to 3.21 for nonfatal
21 myocardial infarction; although I will note that
22 the number of events in some of these analyses is

1 quite small.

2 The conundrum we have with us today is that
3 romosozumab is clearly efficacious. It reduces
4 fractures in women with postmenopausal
5 osteoporosis. It not only reduces some fractures
6 compared to placebo; it does it compared to
7 alendronate, which is a widely used therapy for
8 osteoporosis.

9 This is really the first trial that I'm
10 aware of that in a head-to-head fashion has shown
11 fracture superiority on outcomes against an
12 approved osteoporosis therapy.

13 On the flip side, in these two fracture
14 outcome trials, we have evidence of cardiovascular
15 harm in one of these trials and not in the other.
16 So the question is, is this a true adverse effect
17 of romosozumab or is it a chance finding. Could
18 alendronate in fact have reduced the risk of MACE
19 compared to alendronate in the alendronate-
20 controlled trial and that explains the findings?

21 Through the presentations today, we're going
22 to dissect some of these possibilities and kind of

1 explore these. But at the end of the day, we're
2 not really sure what explains the difference
3 between the trials.

4 So in this context, we also have to remember
5 that the background risk for cardiovascular disease
6 increases after menopause, so if you have a drug
7 that has a true effect, that would further increase
8 this risk.

9 Let me end with the questions that we're
10 going to ask the panel to discuss and vote upon at
11 the end of the day so you can frame things in your
12 mind as you hear all the presentations.

13 We have two discussion questions and one
14 voting question. The first discussion question
15 asks the committee to discuss whether the
16 cardiovascular safety of romosozumab has been
17 adequately characterized. If additional safety
18 data are needed, we'd like the committee to discuss
19 the types of data that are needed and also whether
20 these data should be obtained pre- or post-
21 approval.

22 Question 2 starts with the indication that

1 Amgen is proposing, which, again, is this high risk
2 for fracture indication. Specifically, Amgen is
3 seeking an indication for the treatment of
4 osteoporosis in postmenopausal women at high risk
5 of fracture, defined as a history of osteoporotic
6 fracture, multiple risk factors for fracture, or
7 patients who have failed or are intolerant to other
8 available osteoporosis therapy.

9 So we'd like the committee to discuss
10 whether the benefit-risk profile for romosozumab
11 could be improved by further narrowing the
12 indicated population to patients at low
13 cardiovascular risk, and if so, how to define the
14 narrow population.

15 Really, we're trying to get to -- just
16 saying treat patients with low cardiovascular risk
17 is very fuzzy. So in clinical practice, how is
18 someone going to identify the appropriate patient
19 to treat with this therapy? How do you
20 operationalize the definition of low cardiovascular
21 risk if you think that's something that's important
22 to do?

1 Then we'll end with a voting question, which
2 asks is the overall benefit-risk profile of
3 romosozumab acceptable to support approval? This
4 is a multiple-choice question. Option A is yes for
5 the indication that Amgen is seeking this high risk
6 of fracture indication; B would be yes, but for a
7 different indication; and then C would be, no, that
8 there's no population in whom the benefits outweigh
9 the risks.

10 So we'd like to hear the rationale for your
11 vote, and if you voted for B, which is an
12 indication different to what Amgen is proposing,
13 we'd like you to describe that patient population
14 for whom the benefits outweigh the risks.

15 Thank you for your attention. I'll turn it
16 back to the chair

17 DR. LEWIS: Thank you. I'd like to invite
18 the applicant to the podium to begin their
19 presentations.

20 We'll now proceed with presentations from
21 the applicant. Both the Food and Drug
22 Administration and the public believe in a

1 transparent process for information gathering and
2 decision making. To ensure such transparency at
3 the advisory committee meeting, FDA believes it is
4 important to understand the context of an
5 individual's presentation.

6 For this reason, FDA encourages all
7 participants, including the sponsor's non-employee
8 presenters, to advise the committee of any
9 financial relationships they may have with the firm
10 at issue, including consulting fees, traveling
11 expenses, honoraria, and interests in the sponsor,
12 including equity interests and those based on the
13 outcome of the meeting.

14 Likewise, FDA encourages you, at the
15 beginning of your presentation, to advise the
16 committee if you do not have any such financial
17 relationships. If you choose not to address this
18 issue of financial relationships at the beginning
19 of the presentation, that will not preclude you
20 from speaking.

21 Let's go ahead and proceed with the
22 presentations from Amgen.

1 **Applicant Presentation - Scott Wasserman**

2 DR. WASSERMAN: Good morning, Dr. Lewis and
3 members of the committee. My name is Scott
4 Wasserman. I'm a cardiologist and therapeutic area
5 head for bone, cardiovascular, metabolic, and
6 neuroscience at Amgen. I'd like to thank the FDA
7 for the opportunity to present our data on
8 romosozumab, which we will refer to as romo. We
9 will discuss the benefit-risk of romo for women
10 with postmenopausal osteoporosis, or PMO, at high
11 risk for fracture.

12 Osteoporosis is a progressive disease, often
13 resulting in life-changing fractures. Despite
14 available therapy, women with PMO continue to
15 fracture at an unacceptable rate. With its unique
16 dual mechanism of action, romo offers women
17 superior, near-, and long-term fracture risk
18 reduction.

19 While the benefit is well-established, the
20 cardiovascular or CV risk associated with romo is
21 uncertain. An imbalance in CV events was seen in
22 one phase 3 PMO fracture trial, but not the other.

1 The genetic evidence, phase 1, through non-pivotal
2 phase 3 clinical trial data, and extensive acute
3 and chronic nonclinical data do not support a CV
4 risk with romo. Nevertheless, we cannot exclude
5 the possibility of an increase in cardiovascular
6 risk.

7 This leads to the critical question: is the
8 benefit-risk favorable, assuming that the
9 cardiovascular risk is real? Our benefit-risk
10 analysis shows that the definitive fracture
11 benefits outweigh the potential cardiovascular risk
12 in women with PMO at high fracture risk.

13 If romo is approved, our objective is to
14 ensure a positive benefit-risk profile in clinical
15 practice. We believe that this can be achieved
16 through a targeted indication and labeling for
17 cardiovascular risk, pharmacovigilance, and a
18 postmarketing study to describe the CV safety
19 profile in women in the United States.

20 After my introduction, Dr. McClung will
21 discuss the patients at risk for potentially life-
22 altering fractures. Dr. McClung is a clinical

1 trialist and expert in the care of patients with
2 osteoporosis and bone disorders. Dr. Wagman, the
3 global development leader for romo, will present
4 efficacy.

5 I'll return to present safety and
6 benefit-risk. Dr. Galson, head of global
7 regulatory affairs and safety, will provide Amgen's
8 closing comments. And finally, Dr. Cosman, a
9 clinician and trialist with particular expertise in
10 bone anabolic therapies, will share her perspective
11 on the potential role of romo in women at high
12 fracture risk.

13 Two additional experts are available to
14 answer your questions. Dr. Roe is a cardiologist
15 and cardiovascular clinical trialist at Duke
16 Clinical Research Institute or DCRI. Dr. Sabatine
17 is a cardiologist and chairman of the thrombolysis
18 in myocardial infarction or TIMI study group.
19 Drs. McClung, Cosman, Roe, and Sabatine are serving
20 as paid consultants to Amgen. They have no
21 financial interest in the outcome of the meeting.

22 Romosozumab is a humanized monoclonal

1 antibody against sclerostin. Sclerostin is a
2 protein secreted by osteocytes that inhibits bone
3 formation. By blocking sclerostin, romo stimulates
4 osteoblasts and bone growth while inhibiting
5 osteoclasts and bone resorption.

6 This dual mechanism of action explains the
7 rapid marketed improvement in bone mass and
8 strength and the associated fracture risk
9 reduction. The proposed indication is the
10 treatment of osteoporosis in postmenopausal women
11 at high risk for fracture.

12 To address the observed CV imbalance in
13 study 142, we proposed warning language in the
14 label. This includes a boxed warning that romo may
15 increase the risk of myocardial infarction, or MI,
16 and stroke and to consider the benefit-risk in
17 patients with a prior or possibly recent myocardial
18 infarction or stroke.

19 The intended dosing is romosozumab,
20 210 milligrams monthly for 12 months, followed by
21 antiresorptive therapy. This dosing paradigm was
22 evaluated in the pivotal phase 3 studies.

1 I would now like to introduce Dr. McClung to
2 discuss the unmet need.

3 **Applicant Presentation - Michael McClung**

4 DR. McCLUNG: Good morning. I'm Mike
5 McClung, an endocrinologist from Portland, Oregon
6 and the founding director of the Oregon
7 Osteoporosis Center, where over the past 40 years,
8 I've had the opportunity to care for hundreds of
9 women with postmenopausal osteoporosis.

10 I've been an investigator and published the
11 results of many clinical trials evaluating
12 treatments for osteoporosis and currently serve on
13 the boards of the International Osteoporosis
14 Foundation and the North American Menopause
15 Society.

16 In the next few minutes, I would like to
17 share with you some thoughts about an unmet need in
18 the treatment of women with postmenopausal
19 osteoporosis.

20 As stated, postmenopausal osteoporosis is a
21 chronic condition resulting from progressive bone
22 loss beginning around the time of menopause and

1 continuing into old age in women. This loss of
2 bone mass results in a gradual deteriorating of the
3 structure of trabecular bone, shown here in the
4 slide, and of cortical bone. This results in
5 impaired skeletal strength and predisposes patients
6 to fractures.

7 We evaluate skeletal status by measuring
8 bone mineral density, or BMD, by a radiologic
9 technique called DEXA, a very strong predictor of
10 fracture risk. For every standard deviation
11 decrease in age-adjusted BMD, hip fracture risk
12 increases by 2.6-fold. By combining bone density
13 and other clinical risk factors, women can be even
14 more readily stratified into categories of fracture
15 risk.

16 We diagnose osteoporosis in postmenopausal
17 women who have had an osteoporotic fracture or,
18 based on the relationship between BMD and fracture
19 risk, in those who have a bone density T-score
20 value of minus 2.5 or less. Importantly, recent
21 studies have demonstrated that the level of hip BMD
22 measured on treatment correlates with current

1 fracture risk. The higher the hip BMD achieved on
2 therapy, the lower the risk of fracture.

3 Fractures are the clinical consequence of
4 osteoporosis and they occur commonly. Roughly half
5 of women age 50 and older will experience a
6 fracture related to osteoporosis in her lifetime.
7 Symptomatic fractures of the spine or clinical
8 vertebral fractures, as well as fractures of the
9 hip and proximal humerus, are the most serious and
10 clinically important fractures.

11 Each year, about 300,000 hip fractures, more
12 than 700,000 fractures of the spine, and about
13 200,000 fractures of the proximal humerus occur in
14 the United States, and most of these occur in
15 women. But these dry statistics don't reflect the
16 substantial and often devastating effects that
17 fractures inflict upon individual women and their
18 families.

19 Serious fractures are associated with a
20 2 to 8-fold increase in the risk of death and an
21 excess mortality of up to 30 percent in the first
22 2 years following the fracture. For the survivors,

1 fractures often result in significant alterations
2 in their physical appearance and mobility and in
3 their quality of life, often propelling older women
4 toward frailty, dependence, and depression.

5 Multiple vertebral fractures result in a
6 downward spiral of both physical and psychosocial
7 function. After the second or third vertebral
8 fracture, women experience height loss and
9 kyphosis, chronic pain, and impaired ambulation,
10 transforming them, as several patients have
11 described to me, into old women.

12 Also, thoracic height also impairs
13 cardiopulmonary function, which may contribute to
14 the increased mortality associated with vertebral
15 fracture. A different downward spiral toward
16 frailty can be described following a hip fracture,
17 the most common reason for a woman's admission to a
18 nursing home.

19 Risk factors for fractures in postmenopausal
20 women are very well-characterized, the most
21 important of which is a history of a previous
22 osteoporotic fracture, an event that increases the

1 risk of a second fracture overall by about twofold.
2 But fracture risk is especially high in women with
3 a recent fracture.

4 The data in this graph demonstrate that the
5 risk of a recurrent fracture increases by about
6 fivefold during the first 1 to 2 years following an
7 incident fracture. Ten percent of women who
8 present with a clinical fracture will have another
9 fracture within the next 12 months, and an
10 additional 8 percent will have a fracture during
11 the second year, including 5 percent of women who
12 would experience a hip fracture.

13 Among women with osteoporosis who experience
14 a new vertebral fracture, almost 20 percent, will
15 have an additional vertebral fracture within the
16 next 12 months. Having a major fracture is as
17 close to an emergency as occurs in women with
18 osteoporosis, and there is an urgency in treating
19 patients with recent fractures.

20 Women at high risk of fracture are readily
21 identifiable. This includes, as mentioned, women
22 with previous, especially recent, fractures, but

1 also includes women of advanced age or with
2 multiple comorbidities, including frailty and
3 falls, and women with very low bone density with or
4 without other risk factors.

5 Once a woman at high risk of fracture is
6 identified, we have several drugs that can increase
7 her bone density and bone strength and
8 substantially reduce her fracture risk.

9 The commonly used antiresorptive agents,
10 bisphosphonates and denosumab, inhibit the
11 dissolution of bone by osteoclasts. They increase
12 bone density, but they do not correct the damage to
13 bone architecture that characterizes osteoporosis.
14 As will be shown this morning, many patients remain
15 at high risk of fracture, even a while on
16 bisphosphonate therapy.

17 Teriparatide and abaloparatide are bone
18 anabolic agents that improve bone density,
19 structure, and strength and reduce fracture risk by
20 stimulating new bone formation. There are several
21 limitations to the use of these drugs.

22 The regulatory recommendations limit the use

1 of these drugs to 2 years in a woman's lifetime,
2 significantly impairing our ability to use these
3 agents in the lifelong management of osteoporosis.
4 To maintain the gains achieved with anabolic
5 therapy, these agents are routinely followed by
6 antiresorptive drugs.

7 These data and other information provide a
8 description of what an approved osteoporosis
9 treatment would be, a drug that stimulates new bone
10 formation to quickly increase bone mass and to
11 restore bone architecture, thereby improving bone
12 strength to rapidly reduce fracture risk.

13 This is one of the major unmet needs in the
14 treatment of osteoporosis. We need to do better
15 than we do with our antiresorptive treatments and
16 current anabolic therapies. As you will hear in
17 the presentations to follow, treating
18 postmenopausal women with osteoporosis with
19 romosozumab moves us closer to this improved
20 therapy.

21 Thank you for your attention. I would now
22 like to introduce Dr. Rachel Wagman, who will

1 present the romosozumab efficacy data.

2 **Applicant Presentation - Rachel Wagman**

3 DR. WAGMAN: Thank you, Dr. McClung.

4 My name is Rachel Wagman. I'm an
5 endocrinologist and global development leader for
6 romosozumab. I will now share efficacy results
7 from the clinical development program. I'll focus
8 on three key areas. I'll provide an overview of
9 the clinical development program; I'll explain dose
10 selection and the sequential treatment regimen with
11 a follow-on antiresorptive; and I'll show the
12 clinical data from the phase 3 program in
13 postmenopausal women with osteoporosis, which
14 includes two fracture outcome trials, studies 337
15 and 142, and a bone strength trial, study 289.

16 Even prior to the clinical program, we found
17 that romosozumab had the unique effect of
18 stimulating bone formation while inhibiting bone
19 resorption or breakdown. These data led to a
20 clinical development program of 19 studies
21 involving more than 14,000 participants.

22 While the development program is covered

1 more fully in the briefing document, I will focus
2 on data from the key phase 2 and phase 3 studies
3 supporting the dosing, safety, and efficacy.

4 Let's start with the data supporting the
5 dosing regimen. In study 326, we evaluated a
6 variety of doses by measuring gains in bone mineral
7 density, or BMD, over time. Here is a comparison
8 of monthly doses of 70, 140, and 210 milligrams
9 monthly.

10 We found dose-related increases in lumbar
11 spine BMD. The largest gains in BMD occurred with
12 210 milligrams monthly. We saw increases as early
13 as 3 months and sustained through 24 months of
14 treatment. There was not an exposure safety
15 relationship either with the dose level or dose
16 duration.

17 We chose the duration of 12 months of
18 treatment because the majority of BMD gains
19 occurred during the first year of therapy and the
20 anabolic effect had attenuated by this time point.

21 Anticipating romosozumab might offer
22 improved efficacy compared with existing therapies,

1 we also evaluated BMD gains versus alendronate, the
2 most commonly prescribed antiresorptive, and versus
3 teriparatide, the standard of care bone-building
4 agent. Lumbar spine BMD increases were greater
5 with the romosozumab dose of 210 milligrams monthly
6 as compared with both agents and placebo.

7 While not shown on this slide, we also saw
8 similar findings at the hip. These phase 2
9 findings provided early evidence that romosozumab
10 would lay a foundation of benefit with increased
11 bone mass that we expected would provide
12 significant antifracture efficacy in phase 3.

13 I'll now review our phase 3 studies in
14 postmenopausal women with osteoporosis at high risk
15 for fracture. As the bone-building effect of
16 romosozumab is reversible when treatment is
17 discontinued, we evaluated a sequential treatment
18 regimen to preserve benefit, romosozumab for
19 12 months followed by at least 1 year of
20 antiresorptive therapy.

21 For the multi-year fracture outcome trials,
22 studies 337 and 142, we evaluated two different

1 treatment sequences. In study 337, the follow-on
2 therapy was denosumab, and in study 142, it was
3 alendronate. Study 289 was a 1-year bone strength
4 study that compared romosozumab with teriparatide,
5 the standard of care bone-forming agent. You'll
6 see they're slightly different populations for each
7 of these trials, and I will discuss each study in
8 turn.

9 Study 337 was designed to evaluate safety
10 and efficacy versus placebo. Subjects were
11 randomized to receive romosozumab or placebo for
12 12 months, followed by transition to denosumab
13 antiresorptive therapy for 24 months. Subjects
14 were blinded to their randomized treatment group
15 through end of study. As with all of the trials,
16 study participants received calcium and vitamin D.

17 Inclusion criteria, shown here, were a
18 combination of T-score and fracture status that
19 ensured subjects who had severe disease were not
20 enrolled. The co-primary endpoints were the
21 incidence of new vertebral fracture, confirmed
22 radiographically at 12 and 24 months. Important

1 secondary endpoints included other fracture
2 categories at 12 and 24 months as well as BMD
3 outcomes. We also evaluated fracture outcomes up
4 to 36 months as exploratory endpoints.

5 Baseline characteristics were balanced
6 between treatment groups. Study participants were,
7 on average, 70 years of age with approximately a
8 third 75 years and older. They had osteoporosis by
9 T-score and a fifth had prior vertebral fracture.
10 Eighty-nine percent of subjects completed 12 months
11 and 80 percent completed 36 months.

12 Turning to the results, study 337 showed
13 consistent antifracture efficacy with romosozumab
14 treatment at 12 and 24 months co-primary endpoints.
15 The Y-axis shows the subject incidence of new
16 vertebral fracture and the X-axis, the study month.
17 Absolute risk for fracture is shown above each bar.

18 At 12 months, there was a 73 percent
19 relative risk reduction in subjects who took
20 romosozumab versus placebo. Efficacy was sustained
21 for the entire 24-month period, resulting in a
22 75 percent relative risk reduction with romosozumab

1 followed by denosumab versus placebo followed by
2 denosumab. Secondary fracture endpoints showed a
3 consistent trend in favor of romosozumab, and I
4 will discuss those shortly.

5 Let's now turn to study 142, which compared
6 romosozumab with alendronate. All participants had
7 a prior vertebral or recent hip fracture, and as
8 you heard from Dr. McClung, prior fracture is one
9 of the most important predictors of future fracture
10 risk. Therefore, all study participants received
11 active treatment in this head-to-head study.

12 Subjects were randomized to receive
13 romosozumab or alendronate for 12 months, then they
14 either transitioned to or maintained alendronate
15 for at least an additional 12 months. Subjects
16 were blinded to their randomized treatment group
17 through end of study. Inclusion criteria, shown
18 here, ensured that all subjects were at a higher
19 risk for fracture than in study 337.

20 Primary endpoints were new vertebral
21 fracture, confirmed radiographically at 24 months,
22 and clinical fracture at primary analysis.

1 Specifically, the clinical fracture endpoint
2 includes all non-vertebral fractures plus the
3 vertebral fractures that come to clinical attention
4 through acute symptoms.

5 Primary analysis was prespecified in the
6 protocol to be the time when all subjects had
7 completed the 24-month visit, and clinical
8 fractures were confirmed in at least 330 subjects.
9 Key secondary endpoints included other fracture
10 categories at primary analysis and BMD at 12 and
11 24 months at lumbar spine and hip.

12 As in study 337, baseline characteristics in
13 study 142 were balanced between treatment groups.
14 However, the study participants were older,
15 74 years of age on average. Ninety-six percent of
16 subjects had prevalent vertebral fracture and
17 nearly 9 percent a recent hip fracture; 89 percent
18 of subjects completed 12 months; and 77 percent at
19 primary analysis, which was after a median of
20 33 months of follow-up.

21 I'll now turn to the two primary endpoints
22 of clinical fracture at primary analysis and new

1 vertebral fracture at 24 months. Romosozumab met
2 both primary endpoints in this head-to-head
3 fracture study with statistically significant risk
4 reductions of clinical fracture and vertebral
5 fracture versus alendronate.

6 As shown on the left, at primary analysis,
7 there was a 27 percent relative risk reduction of
8 clinical fracture in subjects who took romosozumab
9 for 1 year followed by alendronate compared with
10 those who maintained alendronate as monotherapy.
11 On the right, at 24 months, subjects randomized to
12 romosozumab showed significantly reduced vertebral
13 fracture by 50 percent.

14 For vertebral fractures, a look back at the
15 earlier time point of 12 months demonstrates the
16 foundation of benefit that romosozumab established
17 in reducing fracture risk. At 12 months,
18 romosozumab reduced vertebral fracture by
19 36 percent versus alendronate.

20 Notably, subjects treated with alendronate
21 still have a risk of new vertebral fracture, 5
22 percent at 12 months and 8 percent at 24 months.

1 Romosozumab cuts that risk in half.

2 Having discussed the primary endpoints from
3 studies 337 and 142, I would like to focus on
4 fracture outcomes looking at time to event. We
5 analyzed fracture endpoints that are associated
6 with morbidity and clinically meaningful for
7 patients. These were predefined endpoints,
8 including clinical and hip fractures, and I'm going
9 to show you outcomes by time to event.

10 These data show consistency of effect in
11 both a high-fracture risk population in study 337
12 and a higher fracture risk population in study 142.
13 First, we'll look at clinical fractures, a
14 secondary endpoint in study 337 and a primary
15 endpoint in study 142.

16 The Y-axis shows the cumulative assessment
17 of clinical fracture and the X-axis the study
18 month. As you can see on the left, in study 337, a
19 high risk for fracture population, and on the
20 right, in study 142, the higher risk for fracture
21 population, and separation of the curves occurs
22 early in both populations.

1 To show consistency of time to event between
2 trials, I am showing 36-month data from study 337
3 and data from primary analysis after a median of
4 33 months in study 142. The differences were
5 clinically meaningful in both studies as early as
6 12 months, and the benefit is maintained after
7 transition to antiresorptive therapy.

8 As we all know, hip fractures are clinically
9 devastating fractures with significant morbidity
10 and associated mortality. In both trials, there
11 were fewer events in those subjects who took
12 romosozumab compared with either alendronate or
13 placebo, and the separation continued through the
14 end of both studies.

15 Notably, in study 142 on the right, hip
16 fractures were reduced by nearly 40 percent versus
17 the standard of care, alendronate. In each study,
18 subjects first treated with romosozumab had fewer
19 fractures than those who were not, reinforcing the
20 benefit of 1 year of romosozumab followed by an
21 antiresorptive.

22 Let's turn our attention to change in BMD, a

1 secondary endpoint in both studies. BMD is a
2 clinical endpoint that clinicians use to understand
3 osteoporosis treatment response. Antifracture
4 efficacy with romosozumab allows us to explore the
5 relationship between fracture reductions and gains
6 in BMD, which are a known measure of bone strength.

7 The Y-axis shows percent change from
8 baseline in BMD, and the X-axis the study month.
9 In study 337, we saw rapid and substantial BMD
10 gains in the total hip, 6.8 percent at 12 months
11 and 8.8 percent at 24 months. In study 142, gains
12 were similar with 6.2 percent and 7.2 percent at
13 12 and 24 months respectively, which corresponded
14 to a mean difference of over 3 percent compared
15 with alendronate.

16 This is an important point because the
17 greater BMD gains with romosozumab compared with
18 alendronate reflect larger increases in bone mass
19 that translated into superior antifracture efficacy
20 in this head-to-head comparison. In both studies,
21 these BMD increases with romosozumab are larger
22 than seen with any other single agent currently

1 available for the treatment of osteoporosis.

2 Let's now move to the final trial. Study
3 289 mimics a common clinical scenario where
4 patients have been treated with a bisphosphonate
5 and remain at high risk for fracture, making them
6 likely candidates for treatment with a bone-forming
7 agent.

8 The focus of this study was to evaluate bone
9 density and strength at the hip using a variety of
10 imaging techniques. Importantly, romosozumab
11 increased bone density and strength compared with
12 teriparatide at both 6 and 12 months. In patients
13 pretreated with a bisphosphonate, previously
14 published data have demonstrated that there may be
15 a delayed response to teriparatide.

16 We similarly observed this finding in our
17 study. As shown on the left, romosozumab led to
18 greater gains in BMD at the total hip compared with
19 teriparatide. Another measurement of clinical bone
20 strength is using FEA or finite element analysis.
21 Since BMD is the major determinant of bone
22 strength, not surprisingly, increases that were

1 assessed by FEA at the hip paralleled those with
2 BMD. These data show that romosozumab builds bone
3 faster than teriparatide at potentially vulnerable
4 sites such as the hip.

5 Romosozumab represents a significant
6 advancement in therapy for the treatment of
7 postmenopausal women with osteoporosis at high risk
8 for fracture. BMD gains at the spine were rapid,
9 increasing by more than 1.5 to 2.5 times over
10 standard of care therapies, teriparatide and
11 alendronate at 12 months.

12 Substantial BMD increases translated into
13 antifracture efficacy in both pivotal fracture
14 outcome trials. Vertebral fracture rates were
15 reduced by 50 percent and hip fractures by nearly
16 40 percent compared with alendronate. One year of
17 romosozumab provides a robust foundation that is
18 maintained with sequential antiresorptive therapy.

19 I'd now like to introduce Dr. Wasserman to
20 discuss the safety of romosozumab.

21 **Applicant Presentation - Scott Wasserman**

22 DR. WASSERMAN: Thank you, Dr. Wagman.

1 I will briefly review safety exposure, the
2 summary of adverse events, and key events of
3 interest. My primary focus will be cardiovascular
4 safety.

5 The romo clinical program provided a safety
6 database of over 14,000 subjects, of which about
7 7,500 received at least 1 dose of romo. The safety
8 results from studies 337 and 142 included
9 approximately 11,000 subjects, of which just over
10 5,600 received at least 1 dose of romo. This
11 represents over 5,000 subject-years of romo
12 exposure in these two studies.

13 During the 12-month period, the overall
14 incidence of adverse events, adverse events leading
15 to discontinuation, and serious adverse events were
16 similar between treatment groups for studies 337
17 and 142.

18 Turning to key events of interest, the
19 number of serious hypersensitivity events was low,
20 but more frequently reported with romo. No
21 anaphylactic reactions attributable to romo were
22 reported. Hypocalcemia events were mostly mild and

1 transient. There was a nadir by month 1 with a
2 return to baseline thereafter. There were no
3 associated symptoms.

4 Osteonecrosis of the jaw, or ONJ, and
5 atypical femoral fracture, AFF, are known risks
6 with antiresorptive therapies. Events were
7 infrequent in both studies. Through month 12, in
8 study 337, there was 1 case of ONJ and 1 case of
9 atypical femoral fracture in the romo group. For
10 the overall study period, 1 additional case of ONJ
11 was observed in the romo group after transitioning
12 to denosumab. In study 142, ONJ and AFF were
13 generally balanced.

14 The overall safety profile of romo is
15 generally consistent with that of other
16 osteoporosis therapies and additional detail was
17 provided in the briefing document. I'll now
18 discuss cardiovascular safety.

19 We'll review the studies, analysis periods,
20 adjudication process, results of the studies and
21 meta-analysis, the supporting data, and provide a
22 conclusion. We'll discuss CV safety in the two

1 pivotal fracture prevention studies, 337 and 142,
2 conducted in women with PMO at high risk of
3 fracture.

4 Data from the 12-month double-blind period
5 allows for a comparison of CV safety between romo
6 and either placebo in study 337 or alendronate in
7 study 142. Data from the overall study period,
8 which includes follow-up on subjects from the first
9 dose of investigational product through end of
10 study, facilitates an assessment of the CV safety
11 of sequential treatment with romo followed by an
12 antiresorptive.

13 The study 142 population was modestly higher
14 cardiovascular risk. They were 3 to 4 years older,
15 had slightly more hypertension, cerebrovascular
16 conditions, ischemic heart disease, heart failure,
17 and atrial fibrillation. Within each study, these
18 characteristics were balanced.

19 Subjects in study 142 were on more baseline
20 CV medications, including beta blockers, ACE
21 inhibitors, and anticoagulants. Within each study,
22 these medications were balanced.

1 Prior to phase 3, based on the theoretical
2 concern from a nonclinical study associating
3 sclerostin inhibition with vascular calcification,
4 we instituted a central adjudication of CV events
5 for studies 337 and 142.

6 DCRI performed this prespecified,
7 independent, treatment-blinded, central
8 adjudication. CV events were identified for
9 adjudication from serious adverse events, or SAEs,
10 based on prespecified preferred terms possibly
11 related to CV events such as chest pain, dyspnea,
12 and ischemic stroke. Adjudication was performed
13 using the CDISC definitions.

14 For the 12-month double-blind treatment
15 period, identification of 345 potential CV SAEs led
16 to 199 positively adjudicated events. From the
17 overall study period, identification of 1,135
18 potential CV SAEs resulted in 686 positively
19 adjudicated events.

20 When the imbalance was detected in
21 study 142, we performed a complete review of the
22 adjudicated studies to ensure a comprehensive

1 understanding of the potential risk. The TIMI
2 study group conducted a second post hoc independent
3 central adjudication. In contrast to the DCRI
4 process, TIMI reviewed all adverse events, totaling
5 over 80,000. These were serious, including fatal,
6 and non-serious adverse events.

7 This process was blinded to treatment and
8 DCRI adjudication. The results were largely
9 consistent in terms of the number of subjects with
10 events, the types of events, and statistical
11 results. Thus, as we agreed with the FDA, we
12 present the prespecified analysis of the DCRI data.

13 Now, turning to subject incidence of events
14 beginning with the 12-month period, the
15 prespecified analyses were based on the composite
16 of positively adjudicated CV SAEs. This composite
17 was prespecified because it encompasses the
18 spectrum of clinically meaningful serious CV events
19 and was anticipated to inform our risk assessment.

20 In the 12-month treatment period of placebo-
21 controlled study 337, the subject incidence of
22 positively adjudicated CV SAEs was 1.3 percent in

1 each arm. In study 142, the subject incidence was
2 1.9 percent on alendronate and 2.5 percent on romo.
3 Approximately 90 subjects in each study had a
4 positively adjudicated CV SAE.

5 After seeing the imbalance in positively
6 adjudicated CV SAEs, we performed a post hoc
7 evaluation of the composite endpoint of major
8 adverse CV events or MACE. MACE was defined as a
9 composite of CV death, MI, or stroke. This narrow
10 composite is typically used in dedicated CV outcome
11 trials evaluating atherothrombotic events.

12 However, studies 337 and 142 were not CV
13 outcomes trials. In the 12-month period, the
14 subject incidence of MACE in study 337 was balanced
15 at 0.8 percent. In study 142, the subject
16 incidence of MACE on alendronate was 1.1 percent
17 and 2 percent on romo. There were approximately
18 60 subjects in each study with MACE.

19 The number of subjects with individual
20 events like MI, stroke, or heart failure at 12
21 months is insufficient to draw conclusions, so our
22 analyses focus on MACE and the composite of

1 positively adjudicated CV SAEs.

2 Turning to the overall study period, the
3 median subject follow-up was approximately 3 years
4 in each study. Over this period, the subject
5 incidence for the prespecified composite of
6 positively adjudicated CV SAEs was generally
7 balanced between treatment arms.

8 There were about 250 to 280 subjects with an
9 event in each trial. In study 337, the subject
10 incidence of MACE in the overall study period was
11 2.4 percent on placebo and 2.7 percent on romo. In
12 study 142, the subject incidence of MACE was
13 5.1 percent on alendronate and 5.7 percent on romo.

14 There were approximately 180 to 220 subjects
15 with MACE in each trial for the overall study
16 period. While there were some numerical
17 differences in individual events like stroke and
18 heart failure, the subject incidence of positively
19 adjudicated CV SAE was generally balanced.

20 Turning to our time-to-event analyses, here
21 are the Kaplan-Meier curves with 95 percent
22 confidence intervals for time to first MACE for

1 study 337 on the left and study 142 on the right.
2 The shaded box denotes the 12-month double-blind
3 treatment period, after which subjects transitioned
4 to antiresorptive therapy. Romo is in blue,
5 placebo in study 337 in gray, and alendronate in
6 study 142 in orange.

7 In study 337, there is no separation between
8 the treatment groups. In study 142, we see an
9 early separation between the romo and alendronate
10 arms. Focusing on study 142, the cumulative
11 incidence of events on romo appears linear before
12 and after the transition to alendronate at
13 12 months. In contrast, the cumulative incidence
14 on alendronate appears non-linear, with an apparent
15 increase at approximately 18 months, despite
16 subjects being on alendronate throughout.

17 Here's the forest plot for time to first
18 event for the 12-month period. Shown are the
19 hazard ratios and 95 percent confidence intervals
20 for MACE, on top, and positively adjudicated CV
21 SAEs on the bottom.

22 The discordant results between studies 337

1 and 142 are apparent on top, shaded in green. The
2 hazard ratio comparing romo to placebo in study 337
3 is 1.03 while the hazard ratio comparing romo to
4 alendronate in study 142 is 1.87. Given the
5 approximately 60 subjects with MACE per trial, the
6 estimated hazard ratios may reflect random high or
7 random low bias.

8 As there is no reason to expect these
9 results to differ and there are approximately 60
10 subjects with MACE per trial, a meta-analysis of
11 the two studies may provide a more precise estimate
12 of the true risk. However, caution is required
13 since there is heterogeneity in the baseline
14 demographics, CV risk, and comparator arms for the
15 two trials.

16 The meta-analysis hazard ratio, based on
17 122 subjects with MACE, is 1.39. Now, adding study
18 1.74, which was a small study in male osteoporosis
19 to the meta-analysis, the hazard ratio increases by
20 0.01 to 1.40.

21 Now, looking at the prespecified composite
22 of positively adjudicated CV SAEs, shaded in green,

1 the hazard ratios are attenuated from those based
2 on MACE. These estimates are based on
3 approximately 90 subjects with events per trial.

4 This result is not completely unexpected,
5 given the inclusion of non-MACE events. However,
6 the majority of non-MACE events are other
7 atherothrombotic events like angina and coronary
8 and non-coronary revascularization, which usually
9 behave like MACE. Thus, the attenuation of the
10 MACE hazard ratio in study 142 from 1.87 to 1.32 is
11 notable.

12 In the overall study period, the MACE hazard
13 ratios and confidence intervals are similar for
14 studies 337 and 142. These estimates are based on
15 about 180 to 220 subjects with MACE in each trial.
16 In study 142, where the potential cardiovascular
17 risk was noted at 12 months, the MACE hazard ratio,
18 based on 219 subjects with an event, is 1.15. With
19 the addition of non-MACE events, the study 142
20 hazard ratio for all positively adjudicated CV SAEs
21 is 1.05.

22 To identify subgroups at increased CV risk

1 with romo, we performed some group analyses,
2 looking at the 12-month MACE data in the
3 meta-analysis. These analyses did not identify a
4 subpopulation at a consistent increased relative
5 risk for MACE. P values for interaction were
6 non-significant for these groups, which included
7 women with prior MI or stroke as well as CV risk
8 factors such as diabetes and hypertension.

9 In a comprehensive effort to identify a
10 biologically plausible mechanism for the study 142
11 results, we looked at the genetic evidence, phase 1
12 through non-pivotal phase 3 clinical trial data,
13 and extensive acute and chronic nonclinical
14 studies, spanning from non-human primates to
15 various mouse models.

16 Importantly, when we look at patients with
17 non-coding variants in the gene-encoding sclerostin
18 that are associated with a modest increase in bone
19 mineral density, we see no increase in early onset
20 CV disease.

21 While these genetic clinical and nonclinical
22 data are not exculpatory, none of these studies

1 identified a biologically plausible mechanism for
2 the discordance between studies 337 and 142 and do
3 not support a CV risk associated with romo.

4 In conclusion, we have discordant results
5 for MACE in the placebo-controlled study 337 and
6 the alendronate-controlled study 142 at 12 months.
7 Considerations include the small number of MACE
8 events in these studies; the non-linear behavior of
9 the alendronate arm in study 142; the attenuation
10 of the 12-month hazard ratio in study 142, with the
11 addition of non-MACE atherothrombotic events; the
12 estimation of risk in the overall study period; the
13 lack of a subgroup at consistent increased relative
14 risk; and the absence of a biologically plausible
15 mechanism from the extensive genetic clinical and
16 nonclinical data.

17 The totality of the data suggests that a
18 potential CV risk may be present, with the
19 meta-analysis MACE hazard ratio of 1.3 at 12 months
20 that decreases to 1.13 in the overall study period.

21 Now, turning to the benefit-risk of romo,
22 the medical need is clear. Despite current

1 therapies, fractures and their adverse impact on
2 women continue. This need is most pressing in
3 women with postmenopausal osteoporosis at high
4 fracture risk.

5 As shown in study 142, despite alendronate,
6 5 percent of women had a symptomatic fracture at
7 1 year, and this nearly doubled to 10 percent by
8 2 years. Marked increases in bone mineral density,
9 or BMD, translate into early and long-term
10 reductions in fracture risk.

11 With appropriate caveats, this cross-study
12 comparison shows the total hip BMD changes for key
13 approved osteoporosis therapies. Denosumab in gray
14 and alendronate in orange are antiresorptive
15 therapies. In turquoise and purple are
16 teriparatide and abaloparatide, respectively, the
17 two bone-forming agents.

18 Now, in blue, you see the rapidity and
19 magnitude of the BMD change with sequential therapy
20 of 12 months of romo followed by denosumab from
21 study 337. These BMD gains with romo are markedly
22 larger than the most powerful bone-forming agent,

1 abaloparatide, and larger than the antiresorptive
2 denosumab.

3 The time to first clinical or symptomatic
4 fracture, one of the primary endpoints of study
5 142, is shown here. Shown in blue is sequential
6 therapy with romo, then alendronate, while
7 alendronate monotherapy is in orange.

8 The curves begin to separate around
9 6 months, with a relative risk reduction of
10 28 percent at 12 months that persists after women
11 transition to alendronate. The absolute risk
12 reduction, and thus, the benefit, grows well past
13 women transitioning from romo to alendronate.

14 Turning to risk, here we've summarized MACE
15 results for the 12-month period on top and the
16 overall period below. Shaded in green, we have two
17 pivotal fracture trials with discordant 12-month
18 MACE results. In study 142, there appears to be a
19 risk of MACE at 12 months. However, the relative
20 risk in the overall study period is 1.15. In study
21 337, there is no imbalance in MACE at 12 months.
22 The hazard ratio of the overall study period is

1 1.12.

2 The totality of data suggests that a
3 potential CV risk may be present in the first
4 12 months. The meta-analysis hazard ratio for MACE
5 at 12 months is 1.39, and it decreases to 1.13 in
6 the overall study period.

7 We are carefully considering the potential
8 CV risk observed in study 142 in our quantitative
9 benefit-risk assessment and proposed real-world
10 observational study. Since there is no consensus
11 on a definitive methodology to quantitate
12 benefit-risk, I'd like to share our assessments.

13 We based our assessment on three key
14 principles. We employed our clinical trial data,
15 not modeling our simulation. Our analytic
16 methodology used all of our data. And lastly, we
17 evaluated a time course that captured a holistic
18 assessment of the benefits and risks.

19 We used data from study 142 where the
20 potential CV risk was observed. This was
21 supplemented by the meta-analysis. Now, recall,
22 study 142 tested the hypothesis that romo, followed

1 by alendronate, reduced the risk of both new
2 vertebral and clinical fractures compared to
3 alendronate alone. The prespecified primary
4 analysis was conducted after subjects were followed
5 for a median of approximately 3 years.

6 Kaplan-Meier incidence, not crude incidence,
7 was used for quantification of the absolute
8 benefits and risks with romo. We evaluated benefit
9 based on two prespecified endpoints, clinical or
10 symptomatic fractures and hip fractures, since hip
11 fractures often have the worst outcomes, including
12 morbidity, loss of independence, and early
13 mortality. We evaluated risk based on post hoc
14 MACE and the prespecified composite of positively
15 adjudicated CV SAE.

16 While we assess benefit-risk quantitatively
17 at the time of the primary analysis, benefit-risk
18 evolves over time. In this figure, on the Y-axis
19 is the excess number of subjects experiencing
20 events, either MACE or clinical fracture, and on
21 the X-axis is the study month.

22 In study 142, the potential risk of MACE, in

1 ruby on the bottom, emerges in the first year and
2 does not appear to increase substantially over
3 time. The reduction in clinical fractures, in
4 purple on the top, also emerges early, but
5 continues to increase over time.

6 We provide our quantitative benefit-risk
7 assessment at 3 years. This correlates with the
8 approximate time of the prespecified primary
9 analysis for study 142 when the benefit-risk of
10 clinical fracture endpoint was evaluated to assess
11 the benefit of sequential therapy.

12 The next few slides explore different ways
13 of comparing specific benefits to specific risks,
14 recognizing that it is difficult to come up with
15 one single right comparison for benefit-risk.

16 Here is the quantitative benefit-risk in
17 study 142, based on the excess number of events
18 after treating 1,000 women with PMO and high
19 fracture risk. On your left is the benefit based
20 on the reduction of clinical or symptomatic
21 fractures and hip fractures. On your right is the
22 risk based on MACE and positively adjudicated CV

1 SAEs in study 142, where the CV risk was observed.

2 Treating a thousand women for 3 years,
3 sequential therapy with romo and then alendronate,
4 prevents 30 clinical fractures and 14 hip
5 fractures. That represents a 1.5 to 3 times more
6 fractures prevented than excess MACE events
7 observed, and 3 to 6 times more fractures prevented
8 than excess CV SAE observed.

9 Using data from study 142, where the CV
10 signal risk is greatest, the benefit-risk of romo
11 is favorable. If the meta-analysis is a more
12 precise estimate of true CV risk, the benefit-risk
13 is even more favorable with approximately 3.5 to
14 15 times more fractures prevented than CV events
15 observed.

16 Are there opportunities to improve on this
17 for the individual patient? From studies 337 and
18 142, as well as an assessment of U.S. Medicare
19 data, we know that approximately 5 percent of women
20 with PMO at high risk of fracture are at high
21 cardiovascular risk based on having a prior MI or
22 stroke.

1 We also know that the 1 to 1 and a
2 half years immediately after an MI or stroke is the
3 highest CV risk period for patients. It drops two-
4 to threefold thereafter and remains stable.

5 These analyses show a similar pattern. On
6 the left is the instantaneous rate of MACE after an
7 MI from an insurance database. On the right is a
8 landmark analysis provided by Dr. Sabatine of the
9 annual rate of MACE from IMPROVE-IT, a recently
10 completed CV outcomes trial in patients
11 hospitalized for an acute coronary syndrome.

12 Both analyses show that the highest rate of
13 MACE is in the 12 to 18 months after the index
14 event. In the real world on the left, this drops
15 from over 9 percent immediately after the event to
16 about 3 to 4 percent annually. In the clinical
17 trial data on the right, it drops from 8 percent in
18 the first year to a stable 2 and a half to 3.5
19 percent per year thereafter.

20 Now, given the uncertainty around the
21 12-month MACE estimate for study 142, it seems
22 appropriate to specifically cite patients with a

1 prior, or more specifically a recent MI or stroke,
2 in warnings and precautions while we acquire more
3 data.

4 We propose a comprehensive pharmacovigilant
5 and risk management plan. This includes continuous
6 signal detection activities from various sources as
7 highlighted on this slide. We are committed to
8 working closely with the FDA to ensure appropriate
9 product labeling, including a proposed box warning
10 for the potential risk of MI and stroke and a
11 medication guide to describe the safety risks to
12 patients.

13 In addition to our routine safety
14 surveillance, we propose a postmarketing, real-
15 world observational study to evaluate the use of
16 romo in the indicated population. In proposing the
17 real-world study, we considered the timing and
18 method for data generation. We believe that a
19 post-approval study is most appropriate, given that
20 the totality of the data suggests that the risk is
21 between 1 and 2 and that the benefit-risk in study
22 142, where the potential CV risk was observed, is

1 favorable.

2 We are proposing an observational
3 postmarketing study that will characterize CV event
4 incidence and assess whether the relative risks are
5 no greater than that observed in study 142. A
6 real-world comparative safety study can do this
7 expeditiously, and, most importantly, can provide
8 this data iteratively in women in the United States
9 with PMO at high risk of fracture who are eligible
10 or receiving romosozumab.

11 The hypothesis of this study is that the
12 relative risk of death, MI, and stroke in U.S.
13 women with PMO at high risk for fracture on romo
14 compared to a matched standard of care cohort does
15 not exceed that observed in study 142.

16 Specific outcomes include a description of
17 these two populations and a comparison of the
18 incidence of death, myocardial infarction, and
19 stroke during the 12-month romo treatment period
20 versus standard of care osteoporosis therapies.
21 Cohorts will be balanced using propensity score
22 methods.

1 Now, the FDA outlined a number of
2 considerations in assessing real-world studies.
3 Amgen has conducted several real-world comparative
4 safety studies, including one for our osteoporosis
5 therapy, denosumab. Using three large
6 administrative health claims databases that
7 encompass Medicare and commercial insurance plans,
8 we've preliminarily identified more than
9 1.4 million women in the United States with PMO at
10 high risk of fracture.

11 We will use validated algorithms and drug
12 codes to identify patients receiving prescriptions
13 for PMO treatment. CV events like MI and stroke
14 are well-documented in these administrative claims
15 databases. Death is also available in these
16 databases and through linkage with the Social
17 Security administrative Death Master File.

18 Covariates, including demographics and
19 concomitant clinical diagnoses and machines, will
20 be ascertained based on international
21 classification of disease and procedure codes.
22 Additionally, we're exploring ways to link these

1 data to additional clinical data sets.

2 Analytic methods are available to mitigate
3 and assess the impact of both measured and
4 unmeasured confounders. And lastly, there is an
5 opportunity to continuously accrue this data and
6 iterate on it. Thus, these observational methods
7 can expeditiously and appropriately address this
8 magnitude of risk, and we look forward to
9 partnering with the FDA to develop these real-world
10 observational comparative safety study.

11 I'll now turn it over to Dr. Steven Galson.

12 **Applicant Presentation - Steven Galson**

13 DR. GALSON: Good morning. I'm Steven
14 Galson. I am the senior vice-president for global
15 regulatory affairs and safety at Amgen. I wanted
16 to note that from 2001 to 2007, I was the deputy
17 director, and then the director of FDA Center for
18 Drug Evaluation and Research, but was not involved
19 in any discussions about this product.

20 As you've heard, in women with
21 postmenopausal osteoporosis at high risk of
22 fracture, there is a need for a rapidly-acting

1 therapy such as romosozumab. We're delighted that
2 romo was recently approved in Japan, and we look
3 forward to working with the FDA to assure its safe
4 use in the United States.

5 For women with osteoporosis, serious
6 fractures may be as consequential as MI or strokes.
7 With romo, the superior fracture risk reduction
8 must be weighed against a possible increased CV
9 risk. We and the FDA have highlighted the
10 scientific uncertainty around this risk. We're
11 confident that the overall favorable benefit-risk
12 relationship observed in the clinical trial can be
13 achieved in the clinic.

14 The possible risk of MI and stroke can be
15 clearly communicated to physicians and patients via
16 a box warning, as they are for other medical
17 products with CV risk. Physicians and patients
18 will need to consider benefit-risk, especially in
19 patients with recent MI or stroke, an easily
20 identifiable population. With appropriate
21 labeling, physicians and patients can share
22 informed decision making based on an individual

1 assessment of fracture and CV risk.

2 Amgen is committed to monitoring the
3 emerging postmarketing safety profile on an ongoing
4 basis. We propose to conduct an observational
5 study to quickly confirm that the risk is not
6 greater than what was suggested by the 142 study
7 and that patients have an acceptable safety profile
8 in actual U.S. clinical practice.

9 We look forward to discussing the labeling
10 with FDA. Information in labeling, including a box
11 warning for patients with prior MI or stroke,
12 particularly recent events, is, we believe, the
13 most fitting way to communicate the potential
14 cardiovascular risk. A boxed warning is to be used
15 when it is essential to consider the risk in
16 appropriate patient selection and treatment
17 decisions.

18 To conclude, the totality of the data in our
19 submission, which included over 14,000 subjects
20 with a total of 400 MACE events, gives enough
21 certainty that the overall benefit-risk is
22 positive. Careful construction of the label will

1 allow women and their doctors to assess
2 benefit-risk and make appropriate choices.

3 Thank you. I'd like to now introduce
4 Dr. Felicia Cosman to provide closing comments.

5 **Applicant Presentation - Felicia Cosman**

6 DR. COSMAN: Thank you, Dr. Galson.

7 For the last 30 years, I've been involved in
8 the clinical research and clinical care of women
9 with osteoporosis, and I feel I have a pretty good
10 sense of what patients with osteoporosis need.

11 Women who have incident osteoporotic
12 fractures are at extremely high risk of more
13 fractures. In fact, almost 1 in 5 will have
14 another fracture within the very next 2 years after
15 the first fracture occurs. We call this a high
16 imminent risk of fracture. There are other women
17 who are at similarly high risk, and we can easily
18 identify them with readily available tools.

19 Women at high risk for fracture need a
20 potent therapy that reduces fractures quickly and
21 prevents their life-altering consequences.
22 Romosozumab provides an answer for these women.

1 With 1 year of romosozumab therapy, all clinical
2 fractures are reduced, and the hip BMD increments
3 that we see with 1 year of romosozumab are more
4 than twice what we see with any other therapy,
5 including currently available anabolic agents.

6 Of course, romosozumab is not appropriate
7 for every woman. Because of the uncertainty
8 regarding cardiovascular risk, as a clinician, I
9 would want to try to avoid using it in people who
10 appear to be at high absolute risk for these
11 events. For now, certainly until further data
12 accrue, I would avoid or at least certainly delay
13 using romosozumab in women who have had a recent
14 heart attack or stroke.

15 In all patients, I would want to engage in a
16 conversation regarding potential benefits and risks
17 that has to be individualized, of course, based on
18 their underlying medical history, and there are
19 other personal concerns. But keep in mind, these
20 are conversations that physicians have with their
21 patients regarding all therapeutic interventions
22 that are being considered.

1 I think the key clinical message here is
2 that if we target romosozumab treatment to the
3 women at highest risk for fracture, particularly
4 those at high imminent risk for fracture, and avoid
5 using it in people who are at highest risk for
6 cardiovascular events, we can expand the distance
7 between benefit and risk and optimize the
8 effectiveness and the safety of this powerful
9 medication.

10 The unique potential of romosozumab is its
11 ability to quickly repair the skeletal defects
12 associated with osteoporosis and to restore
13 skeletal integrity. For women with an urgent need,
14 especially those women who have recent fractures,
15 romosozumab treatment could change their clinical
16 course and interrupt the downward spiral toward
17 immobility, disability, and loss of independence.

18 Thank you.

19 **Clarifying Questions to Applicant**

20 DR. LEWIS: Thank you.

21 At this point, we're going to open the time
22 for clarifying questions from the committee

1 members. If you'll just sort of raise your hand,
2 we'll get your name and try to get everybody in
3 order. I also want to remind you that we will have
4 time for discussion later on, so please try to make
5 this more of a clarifying question just to kind of
6 keep us on time.

7 I do want to remind you to please state your
8 name for the record before you speak and identify
9 which presenter your question is for if that's
10 appropriate or if it's a general question to all
11 presenters. We'll start with Dr. Shaw.

12 DR. SHAW: Thank you. I have two clarifying
13 questions. The first is -- and I'm going to have
14 to make sure I track the person's name, who
15 discussed the risk-benefit trade-off. And you
16 presented -- I think that was the second to last
17 speaker, I believe.

18 I think it was Dr. Galson who presented the
19 assumptions for that risk-benefit analysis, and it
20 was a slide where you summarized the number of
21 prevented fractures with and without romo, and then
22 you had the number of cardiovascular events with

1 and without romo.

2 So my question is, one of your assumptions
3 was, for that calculation, you had used the
4 Kaplan-Meier estimates. I noticed earlier you were
5 using, and probably appropriately, more
6 appropriately, the cumulative incidence, because
7 when you have deaths, you don't want to censor
8 deaths when estimating the potential number of
9 fractures that may be prevented after a death.

10 So there might be a slight optimism. I
11 guess my clarifying question is, did you do it both
12 ways? Did you consider using cumulative incidence
13 curves to predict the number of prevented
14 fractures, which would then not let fractures be
15 prevented after death?

16 It's a little bit of a technical question.
17 I apologize for that. But there's a small number
18 of deaths on both arms, so perhaps this optimism is
19 slight. But I just wanted to ask the team had they
20 considered that change in their risk-benefit
21 analysis.

22 DR. WASSERMAN: Sure. I will address the

1 issue around the benefit-risk as it relates to the
2 cardiovascular events, and then I'm going to ask my
3 statistician to come up and talk about the fracture
4 part and how that was done.

5 I can say that when we look at the
6 Kaplan-Meier versus the subject incidence -- and I
7 actually have the numbers in front of me because as
8 we were preparing, I was wondering about that as
9 well.

10 The actual Kaplan-Meier incidence makes it
11 look a little worse than the subject incidence
12 for --

13 DR. SHAW: For the cardiovascular, right.

14 DR. WASSERMAN: -- the cardiovascular.

15 I will now turn it over to Dr. Milmont to
16 discuss the effect of Kaplan-Meier versus accrued
17 subject incidence on fracture.

18 DR. MILMONT: Hi. I'm Dr. Milmont. I'm the
19 biostats lead for romosozumab. In the assessment
20 of the Kaplan-Meier incidence for the benefit side
21 and fracture, we censor to the time of fracture.
22 So if they died prior to having a fracture, they

1 were censored when they died.

2 I don't know if that clarifies your
3 question.

4 DR. SHAW: Perhaps let me clarify my
5 question for you. So by censoring, if they died
6 before a fracture, what the Kaplan-Meier does is
7 assumes that the people who are censored, the risk
8 of fracture is the same for censored individuals
9 versus people who are not censored.

10 So what that means is you're allowing people
11 who are censored because of death to receive the
12 benefits of the fracture reduction, which can't
13 really happen. So you probably have
14 slightly -- for the same reasons that was explained
15 by Dr. Galson, that you might have been
16 conservative in your -- I guess, actually, you
17 would have had slightly worse cardiovascular
18 tradeoffs and actually slightly less benefit.

19 DR. MILMONT: Right.

20 DR. SHAW: So I just want to point out
21 that's a limitation of your calculation, I believe,
22 but you guys can think about that, to what

1 extent -- it sounds like you did not consider that.
2 You might want to consider that. I think the
3 changes will be minor because of the small number
4 of deaths relative to the number of fractures.

5 My second clarifying question that I wanted
6 to ask -- and I think it involves the same two
7 people, and probably in the same order -- is I
8 appreciated the very careful thought to the
9 postmarketing analysis where you would use, say,
10 administrative health records such as Medicare,
11 these databases, to try to understand the risk.

12 My question to you is, had you thought about
13 this, which might be a very big challenge, I think,
14 for you in doing this survey, that by putting a
15 black box warning -- and we heard our last speaker
16 say what this is going to do is doctors are going
17 to avoid this drug if the women have a recent MI or
18 other concerns about cardiovascular risk.

19 So what that will do is create an indication
20 bias that the women who are prescribed romo will be
21 at lower risk for cardiovascular events. So on one
22 hand, this will be somewhat of a benefit to your

1 analysis in that you won't see too many events, but
2 you'll know and you've already mentioned that you
3 will do these propensity matching analyses to try
4 to undo that bias.

5 So my question to you is, have you guys
6 considered to what degree that is going to expand
7 the uncertainty of your analysis? What might
8 predictably happen, especially if there's a really
9 large avoidance of this drug in people with risk,
10 is you may not be able to rule out the factor of 2
11 simply because of the uncertainty of the
12 sensitivity analyses, and the propensity score, and
13 the unmeasured confounding. Those compulsory
14 analyses will actually just potentially explode
15 your confidence intervals.

16 So have you guys thought about that in your
17 plans to do this analysis?

18 DR. WASSERMAN: We have. Let me try to
19 address it a little bit, and then I'll ask Dr. Roe
20 to come up and comment, because he's had some
21 experience in doing these types of analyses. But
22 you are exactly correct, and it's one of the

1 challenges, obviously. Depending on what the label
2 shows, it will affect how the drug is used in the
3 United States.

4 I would say, though, that for us, the
5 purpose of doing the real-world observational study
6 is to actually make sure that we adequately capture
7 what's going on in clinical practice. That is the
8 primary issue that we have. We have a very clear
9 certain benefit and uncertain risk, and how the
10 drug gets used is very, very important as we go
11 forward. It's most important that we clarify what
12 that risk is in the women that are getting it, but
13 I'll ask Dr. Roe to come up.

14 DR. ROE: Matthew Roe from the Duke Clinical
15 Research Institute. I think the issue of avoidance
16 bias is an important one to consider in an
17 observational study, recognizing that the incidence
18 of prior MI or stroke is low in the patient
19 population of interest, as was shown, but the
20 actual use of therapy in the diverse U.S.
21 population and the safety of that is something
22 that's very important to ascertain early on and

1 iteratively, as Dr. Wasserman said, with an
2 observational study.

3 Whether or not that would address the
4 question in this specific population of patients
5 with prior MI or stroke will depend upon how
6 physicians choose to use the therapy. With the
7 black-box warning, it will indicate that there may
8 be an increased risk, and we know that those
9 patients have the highest absolute risk, especially
10 during the recent period or after the ischemic
11 event. But how the drug is used in practice and
12 the actual safety in the overall population is also
13 a question of great interest that has been raised.

14 So I believe that with the proposed study
15 and the methods used, also accounting for the
16 recently released FDA framework for real-world
17 evidence generation, that this is the most
18 appropriate study to expeditiously assess the
19 potential CV risk in U.S. practice.

20 DR. LEWIS: Thank you.

21 Now, in order to get as many people as
22 possible to ask their question, I'm going to ask

1 people to limit themselves to only one question.
2 We're going to go with Dr. Suarez-Almazor and then
3 Dr. Lincoff.

4 DR. SUAREZ-ALMAZOR: Thank you for your
5 presentation. I had a question with respect to
6 study 142 and the time to event for cardiovascular
7 events. I'm assuming that was not adjusted for
8 baseline characteristics, and although the group
9 seemed to be quite balanced, there was a difference
10 of about 1.5 to 2 percent with more baseline
11 cardiovascular disease in the romo group.

12 I was wondering if you had done the adjusted
13 analysis and what happened to the hazard ratio.

14 DR. WASSERMAN: Dr. Milmont?

15 DR. MILMONT: We have looked at that, and in
16 general, we did not see that any of the baseline
17 characteristics change the hazard ratio from the
18 main analysis.

19 DR. LEWIS: Thank you. Dr. Lincoff?

20 DR. LINCOFF: Thank you. In slide CV-22,
21 where you present the risk subgroups for MACE, it's
22 very interesting, not as much for the relative risk

1 reduction, which obviously is very similar, but it
2 does identify the patients that have the highest
3 absolute risk or the absolute risk increases, prior
4 MI and stroke, which is supportive of your ideas of
5 how you might black-box warning.

6 I was wondering if you had a similar
7 analysis or could generate for concomitant
8 pharmacology therapies that might be associated
9 with reducing risks, such as statins or
10 antiplatelet therapy. It would be interesting to
11 see what the absolute risks were and if that
12 moderated the outcomes.

13 DR. WASSERMAN: It's a very good question,
14 particularly as it relates to this population,
15 because when I showed you the overall population,
16 personally as a cardiologist, the use of what we
17 deem life-saving therapies was not optimal.

18 However, when we look at the population that
19 are actually using those drugs in our clinical
20 trial, what we found is that when we look at
21 patients that have atherosclerotic cardiovascular
22 disease, about 50 percent are on beta blockers;

1 60 percent are on antiplatelet agents; and about
2 40 percent on ACE inhibitors; and 40 to 50 percent
3 were on statins.

4 Now, it's higher than what was seen in the
5 overall population, but better than we typically
6 see in real-world administrative databases. But we
7 have not done the exact analysis that you're asking
8 for.

9 I will say that we've done -- outside of
10 that one analysis, we've done every analysis
11 possible. Like the preceding one, one of the
12 things that we know -- she asked about the
13 adjusting for the various kind of factors at the
14 beginning.

15 One of the things that we did do,
16 interestingly, is we actually looked at
17 discontinuation rates, patients that discontinued
18 in the first 12 months in particular. What we
19 found is that of the demographics of the people
20 that discontinued, they tended to be a little bit
21 sicker in both arms. But what was a little bit
22 surprising, particularly in study 142, is that the

1 patients that had a history of prior MI or stroke,
2 that were randomized to alendronate, there were a
3 lot more of those drop-outs.

4 So what we feel good about is that it's
5 unlikely that the risk that we saw at 12 months is
6 worse, and when we do some sensitivity analyses
7 around that, it actually gets markedly better.

8 So outside of your one question, we've done
9 every analysis.

10 DR. LEWIS: Thank you. Dr. Nahum and then
11 Dr. Blaha.

12 DR. NAHUM: Thank you. Dr. Nahum. I have a
13 question about something in the briefing document.
14 On page 27, there's a figure 8 that relates to
15 dose-finding study 326. And there's an analogous
16 slide, actually, that I'd like you to put up, which
17 is CE-4, also relating to study 326, that is
18 entitled, "Supports Dose of 210 Milligrams Q-Month
19 for 12 months." Yes, that's it.

20 My question is the following. It's clear
21 that this study went from 70 to 140 to 210
22 milligrams q-monthly. First, there was a doubling

1 from 70 to 140; then the factor was 1.5 from 140 to
2 210. And if you look at the slide and the briefing
3 document on page 27, figure 8, it's also clear
4 that, at 24 months, the delta between the treatment
5 effect of the 70 and 140 milligrams dose is about
6 double what the treatment effect difference is, the
7 delta between the 140-milligram to the
8 210-milligram dose. So it would appear that
9 there's an absolutely linear treatment response
10 with increasing dose.

11 There's also a statement in the briefing
12 document under section 6.2, and I'll quote it. It
13 says, "The incidence of adverse events in the
14 phase 2 study was not dose related, and the
15 incidence of neutralizing antibodies against romo
16 was low and similar across doses." And the
17 conclusion there is, thus, "the safety and
18 tolerability of the 210-milligram monthly dose was
19 similar to the lower doses."

20 So I'm assuming that you didn't stop at
21 210 milligrams for any safety or tolerability
22 issue. My question, my clarifying question, is

1 since there appears to be a linear dose response
2 and since there does not appear to be any increased
3 difficulty with safety or tolerability, why was
4 this dose-finding study limited to only
5 210 milligrams, and why wasn't it continued upward
6 to generate even larger treatment effects?

7 DR. WASSERMAN: Sure. Very, very
8 briefly -- because I was actually the one that made
9 those decisions back in 2005, or something like
10 that, or 2006 -- wait, no. I take that back. It
11 was about 2008, 2009.

12 At the time, with biologics, our typical
13 kind of formulation was about 70 mgs per mL for
14 this type of study, and there was a concern over
15 what would be tolerable in terms of a number of
16 injections. So at 210, it was 3 injections.

17 People weren't very excited about that, so
18 subsequently, we've gotten them more used to a
19 larger number of injections, but at the time, that
20 was felt to be kind of the optimal that we could
21 do. So that was the rationale. It's very
22 satisfying. Yes.

1 DR. LEWIS: Thank you. Dr. Blaha and then
2 Dr. Gerhard.

3 DR. BLAHA: Thanks. Mike Blaha. I have a
4 very simple question from a cardiologist's
5 viewpoint. I'm certainly not a bone specialist. I
6 was thinking about how these things work.

7 My question was -- and I just don't know
8 this -- when you increase someone's bone density,
9 for example the dramatic increases on this therapy,
10 is there any change in quality of life or physical
11 activity or exercise associated with this, or is
12 this not perceived by the patient?

13 The reason why I'm asking is I'm just
14 curious if any play on increased cardiovascular
15 disease could be attributable to increased physical
16 activity or something like that, due to the
17 therapy, indirectly, but just a question.

18 DR. WASSERMAN: Dr. Wagman, can you address
19 this question, please?

20 DR. WAGMAN: With increases in bone mineral
21 density, we are not familiar with increases in
22 patient activity or their reports of increased

1 activity.

2 DR. LEWIS: Thank you. Dr. Gerhard and then
3 Dr. Wang.

4 DR. GERHARD: Tobias Gerhard. My question
5 is also for Dr. Wasserman. I apologize that I
6 can't look at you while I ask the question since my
7 back is to you. My questions relate also to the
8 planned or proposed observational studies, so just
9 a clarification first.

10 The way I read this, although you defined
11 this as a prospective observational study, what
12 you're planning to use is really existing automated
13 data resources. In that sense, it's really
14 analogous to a traditional retrospective study.
15 There is no prospective data collection, as I see
16 the proposal. So that's a clarification.

17 The question really is, have you considered
18 something along the lines of a large simple trial,
19 where you combine the use of large databases with
20 randomization at baseline? That question really
21 follows from or builds on Dr. Shaw's comments
22 regarding the channeling or avoidance bias

1 questions because I would be very concerned about
2 an observational study in this setting.

3 I do observational studies for a living. I
4 spent my career arguing for the appropriateness of
5 observational studies to find unbiased results.
6 And here, I don't think -- this is the classic
7 example where observational safety studies fail,
8 where you have a warning in the label that channels
9 the people at higher risk away from the use of the
10 drug, and what you'd expect in all situations,
11 then, is that the drug looks safe because the
12 people at highest risk avoid the drug.

13 The ability to completely adjust for this
14 would require close to perfect measurement of
15 cardiovascular risk at baseline, which with these
16 types of data resources can be controlled to some
17 extent but certainly not fully. So whatever
18 finding you have at DMD [ph], the question of
19 whether the result is correct or biased towards the
20 null remains and cannot be resolved.

21 DR. WASSERMAN: Yes. So thanks for your
22 question. It's something that we have entertained.

1 I think a large simple trial basically has a lot of
2 the same challenges that doing a cardiovascular
3 outcomes trial would.

4 Again, the challenge that we have and the
5 challenge that this committee has is the benefit
6 certain and there's a potential risk. What we're
7 trying to do is further characterize that risk in
8 the patients that are receiving it in the United
9 States in the real-world setting, and ideally
10 hopefully capture the diversity of the United
11 States population that are receiving this drug.

12 As we've thought about this, I think doing a
13 randomized kind of large simple trial, not only is
14 it going to be challenging because, in general,
15 it's the same issue that you're talking about; we
16 would have to enrich the population ideally.

17 You could do a large simple trial and just
18 randomize patients based on whether someone's going
19 to write them a prescription or not, but I think,
20 in general, we're still going to be in that
21 situation where there's that channeling bias.

22 So if they're just writing a prescription

1 for romo, how are you thinking about it?

2 DR. GERHARD: That's where the
3 randomization -- the treatment would be randomized,
4 whatever your population that's chosen, we can
5 discuss, but it's a randomization at baseline, but
6 then everything else is predominantly but not
7 necessarily exclusively relying on the automated.
8 So you could follow up people with the Medicare
9 data and then pull the electronic health records
10 for people that have -- something like that.

11 DR. WASSERMAN: I'm going to have Dr. Roe
12 address this because he has got a lot of experience
13 in this.

14 DR. ROE: I'll state that I'm currently
15 leading a study parting with PCORI, doing this
16 exact thing, testing different doses of aspirin for
17 patients with chronic coronary artery disease. So
18 I have experience in this area, and I believe that
19 a large simple trial would be difficult to do for
20 several reasons.

21 One is I don't believe there's equipoise on
22 the basis of providers who would be prescribing

1 this therapy such that they would feel comfortable
2 randomizing patient to placebo in that type of
3 matter. At least, that's my personal opinion.

4 Secondly, I believe, in a large simple trial
5 that would be done open label, there'd be an
6 expected high rate of crossover because I believe
7 patients would actually request to be on this
8 therapy if they're randomized to placebo in that
9 matter.

10 Then thirdly, as Dr. Wasserman said, there
11 are biases in who's enrolled in a clinical trial,
12 even if it's a large simple trial. So you have to
13 have investigators. You have to have clinical
14 sites who are enrolling patients. And the
15 investigators have to decide which patients who
16 they would approach for inclusion in the trial, and
17 that is already a huge bias that is implicit and we
18 see even in large simple trials such as the one
19 that we're currently conducting.

20 So while tantalizing, I believe that that
21 type of study would not truly address the issue at
22 hand and would have limitations as I've described.

1 DR. LEWIS: Dr. Wang and then Dr. Bauer.

2 DR. WANG: Dr. Wasserman, I just wanted to
3 follow up on this question of the different control
4 arms in your two large phase 3 studies, and the
5 question in 142, whether it's possible that the
6 alendronate arm had a lower cardiovascular risk
7 rather than the romo arm having a higher
8 cardiovascular risk.

9 Based on the risk factor levels at baseline
10 in 142 and whatever data you had regarding those
11 risk factors, were the predicted event rates at
12 either 12 or 36 months, did you have a sense of
13 whether they were high in the romo group, or low in
14 the alendronate group, or was it hard to tell?

15 DR. WASSERMAN: I'm going to ask
16 Dr. Sabatine to address this. We've spent a lot of
17 time looking at that.

18 DR. SABATINE: Yes, an excellent question,
19 indeed; we have spent a lot of time contemplating
20 that, and your question is spot-on. Obviously,
21 there are important differences between 337 and
22 142, and as you rightly noted, in 142, it's not

1 placebo controlled but alendronate controlled.

2 When we re-adjudicated the data and then
3 looked at the results and saw the imbalance, we
4 went through, much like the FDA did, three
5 possibilities, one being could there be an
6 increased risk with romo. But we didn't see it in
7 337. And as Dr. Wasserman nicely covered, the
8 genetic and the preclinical data don't really point
9 to a clear mechanism.

10 Then the second possibility is what you've
11 outlined; could there be a protective effect for
12 alendronate? I think two things to think about for
13 that, one is, at least in RCTs of bisphosphonates,
14 we haven't seen that risk.

15 If we could have a slide for that, for
16 cardiovascular events for bisphosphonates. Slide
17 up, please. This covers all the bisphosphonates,
18 and this covers total adverse cardiovascular events
19 with about 750 events. There are subsets for this
20 meta-analysis with MI and stroke, but they look
21 identical with an odds ratio that's about 1.0, and
22 you can see alendronate contributes a decent amount

1 to this.

2 The other thing, then, is if we look at the
3 142 arms and we look at the experimental arm and
4 the control arm, slide up, on the left-hand side,
5 we have the romo-alendronate arm. There, the event
6 rate is linear.

7 If we were to postulate that alendronate was
8 protective, we might think at the 12-month mark
9 there'd start to be some flattening out of that
10 curve if you suddenly introduced a protective drug,
11 but you don't see that.

12 What did catch our eye is, on the right-hand
13 side of the slide, for patients who are on
14 alendronate for this entire time, stable patients,
15 there should be a linear event rate, it's not. So
16 there's almost no events in the first 3 months,
17 and, as Dr. Wasserman noted, the event rate is low
18 and then starts to increase at the 18-month mark.
19 At around 3 years, the event rate's around 5.1
20 percent. You would expect, then, that at about 1
21 year, it should be 1.7, but it's not. It's 1.1.

22 Slide up, please. With that, then, I think

1 another approach and what we did when we looked at
2 the data was say in the control arm, there's really
3 no reason why it's not linear.

4 So let's take the totality of the data,
5 where you have over 100 events and not tether
6 ourselves to just 20 events at 12 months. If you
7 do that, you generate what the red line is there.
8 Then, instead of it being 1.1 versus 2.0 percent,
9 it's actually 1.6 versus 2.0.

10 Then, my concern is that the event rate in
11 the control arm is a bit of an underestimate just
12 through play of chance. Therefore, the hazard
13 ratio at 12 months is a bit of an overestimate. So
14 if you then use the totality of the control arm
15 data, then that hazard ratio on 142 goes down to
16 around 1.3. And you put that together, then, with
17 337, and then the hazard ratio is around 1.2, and
18 that's not very different than the overall period
19 hazard ratio, which is about 1.1.

20 So in looking at the totality of the data, I
21 think the one outlier, if you will, is that control
22 arm just at the 12-month mark. That's my

1 interpretation of the data.

2 DR. LEWIS: Thank you.

3 Dr. Bauer and then Dr. Kushner.

4 DR. BAUER: I just have a couple questions,
5 really, more related to the skeletal outcomes. I
6 wanted to ask specifically about what happens when
7 the drug is stopped. I know that there was some
8 data about that. But again, given the likelihood
9 that the label will say followed by an
10 antiresorptive therapy, I'm interested to know a
11 little bit more about what happens when you stop.
12 And particularly, given that one of the indications
13 is among those that are intolerant to other
14 antiresorptive therapies, I think that's an
15 important consideration.

16 Then I had just a couple of quick questions.
17 I want to confirm that MACE did not include heart
18 failure. That was a little bit confusing to me.

19 DR. WASSERMAN: MACE is cardiovascular
20 death, MI, and stroke.

21 DR. BAUER: Okay. And I hope the FDA's
22 analysis was similar. Okay. That's good news.

1 Thank you.

2 Then I do have another quick question, which
3 maybe you can come back later, but I'm so happy to
4 see that you did absolute risk in the presentation
5 because it wasn't in the documents before, and it
6 was unfortunate. And I think that's a really
7 important thing that we need to come back to and
8 talk later, but we'll have more time, I'm sure.

9 DR. WASSERMAN: Agreed. Dr. Wagman?

10 DR. WAGMAN: Dr. Bauer, because romosozumab
11 is reversible, it doesn't bind with high affinity
12 to hydroxy appetite, and what we see is there are
13 declines in bone mineral density with treatment
14 cessation.

15 DR. BAUER: Could he just say over what
16 period of time; so 1 year, 2 years, or back to
17 baseline?

18 DR. WAGMAN: Slide up, please. This is from
19 study 326. We found that, in this, we had extended
20 our phase 2 study a few times, and we did have a
21 treatment group where we did have treatment
22 cessation. And you can see that over a 1-year

1 period, there is a slow decline in the BMD, and it
2 is not yet approaching baseline by 1 year off
3 therapy.

4 DR. LEWIS: Thank you. Dr. Kushner and then
5 Ms. Compagni-Portis.

6 DR. KUSHNER: Excuse my voice. I was
7 curious about the estimate of the enrollment for
8 the observational study. Drug uptake, you
9 estimated 8,000 patients, but this could vary.
10 What time period and what numbers are you actually
11 basing that on?

12 DR. WASSERMAN: Yes. That 8,000 women on
13 romosozumab in the Medicare database in 2 years is
14 based on another drug that we have in the
15 osteoporosis area, and then because of the
16 potential for the way the labeling may work out, we
17 handicapped that. So we tried to be a little bit
18 on the conservative side.

19 But you're spot-on. I think our ability to
20 execute this and address this question in a timely
21 fashion is very dependent on people using the drug.

22 DR. LEWIS: Thank you. Ms. Portis and then

1 Ms. Orza.

2 MS. COMPAGNI-PORTIS: I believe FDA usually
3 requires that 25 percent of the enrolled are from
4 the U.S., and that's not true here. So I'm curious
5 about that and this whole picture of the fact that
6 most of the study participants are not U.S. I know
7 that you already are approved in Japan, but we're
8 looking at a very different population, probably
9 higher cardiovascular risk, more obesity in this
10 country.

11 So those are my concerns. I wonder if you
12 can speak to that.

13 DR. WASSERMAN: Oh, absolutely. Are you
14 concerned about efficacy? Are you concerned about
15 safety? Help me understand.

16 MS. COMPAGNI-PORTIS: I'm concerned about
17 efficacy and safety because we're just looking at
18 the cardiac risk, it could be much higher here with
19 our population, and just differences overall in the
20 population and how that affects both efficacy and
21 risk.

22 DR. WASSERMAN: Thanks for that. It's a

1 really important point, so I'm glad you brought it
2 up. We did look at this, in particular, as it
3 relates to the regional differences.

4 Slide up. Before I go into this slide, I
5 just want people to be cautious because the numbers
6 of events that we're dealing with here are small.
7 As we start doing subgroup analyses, 1 or 2 events
8 can make your hazard ratio jump all over the map.

9 This is a meta-analysis because it has the
10 122 MACE events for the 12-month period and 400 for
11 the overall study period. You can see that the
12 majority of our patients in the meta-analysis came
13 from basically central or Latin America as well as
14 central/eastern Europe and the Middle East.

15 You can see that by region, there does not
16 appear to be a marked increase in MACE. I think
17 one of the strengths of the proposed real-world
18 comparative safety study is, as you pointed out,
19 which is something that is very important to us,
20 that we can do a study in the United States and
21 really reflect the diversity of the women in the
22 United States that are using this therapy.

1 I'd like to call Dr. Wagman, if she can, to
2 address the efficacy question.

3 DR. WAGMAN: As Dr. Wasserman pointed out,
4 we similarly had questions in looking at efficacy.
5 As you noted, and as Dr. Wasserman noted, we
6 enrolled a global population. We found that the
7 clinical characteristics were similar in baseline
8 between U.S. and global subjects. We found BMD
9 responses were similar across geographies as was
10 the antifracture efficacy.

11 Slide up, please. This is looking at
12 study 337, and again, a similar geographical
13 distribution to what Dr. Wasserman described. And
14 you can see, for both lumbar spine as well as total
15 hip, we see similar efficacy when it comes to BMD
16 outcomes.

17 Next slide, this is looking at fracture
18 outcomes in study 337 by region; again, similar
19 outcomes across regions.

20 DR. LEWIS: Thank you . Dr. Orza and then
21 Dr. Weber.

22 DR. ORZA: My question is related to the

1 previous one. I was just curious as to why there
2 were so few patients included in the U.S. in the
3 global development program, what the rationale was
4 for that. Also, when you mentioned that it was
5 approved in Japan, I'm just curious what their
6 labeling looks like, what's the indication, and is
7 there a equivalent of a black box, and how did they
8 manage the risk-benefit concern.

9 DR. WASSERMAN: Sure. In terms of the issue
10 around why there was such a small representation of
11 the United States, having done a lot of clinical
12 trials over the course of my career, it's becoming
13 increasingly difficult in the United States to
14 conduct clinical trials. We can get sites up and
15 running and get them -- but patients aren't
16 participating like they participate in other
17 places. It's unfortunate.

18 Then the second part of your question was
19 about Japan? So I'm going to ask Dr. Galson to
20 discuss the label in Japan.

21 DR. GALSON: Yes. In Japan, it's approved
22 for postmenopausal osteoporosis in women at high

1 risk of fracture. There isn't a boxed warning.

2 DR. LEWIS: Thank you. Dr. Weber and then
3 Dr. Rosen.

4 DR. ROSEN: Yes. It's just me, Dr. Rosen.

5 DR. LEWIS: Oh, I'm sorry.

6 DR. ROSEN: It's all right.

7 This is for Dr. Wagman. Excuse my voice.

8 Can you give us some clarification -- I think it's
9 slide 16 -- on the efficacy in non-vertebral
10 fractures, nonclinical fractures, but non-vertebral
11 fractures? Do you have a graph of that? Because
12 there's some disparity between this statistically
13 significant reduction in clinical fractures, which
14 includes non-vertebral fractures, but almost
15 90 percent of those fractures are non-vertebral
16 fractures.

17 So can you give us some clarity about that
18 in 337 and also 142?

19 DR. WASSERMAN: Sure. Dr. Wagman?

20 DR. WAGMAN: Dr. Rosen, we've done that
21 assessment that you asked about.

22 Slide up, please. On the left, you see

1 study 337, and on study 142, as shown on the right,
2 these show the subject incidence rates on your
3 Y-axis and the study month is on the X-axis. And
4 you can see the 25 percent relative risk reduction,
5 this was not significant, as was noted by Dr. Joffe
6 in his introductory remarks.

7 Any questions about the antifracture
8 efficacy for nonvertebral sites, -- that question
9 was answered in study 142, where indeed, at the
10 primary analysis, we did see statistically
11 significant greater reductions in anti-fracture
12 efficacy for non-vertebral sites in those treated
13 with romosozumab followed by alendronate compared
14 with alendronate as monotherapy.

15 DR. ROSEN: Right, but at 1 year, it was not
16 significant.

17 DR. WAGMAN: That was the
18 intended -- prespecified analysis as time point was
19 primary analysis. Also, you can see, though, to
20 your point, even at 12 months, you can see that
21 there is a trend in the separation where there
22 seems to be fewer fractures in those treated with

1 romosozumab.

2 DR. LEWIS: Thank you. We'll have time for
3 discussion and commentary later.

4 Can I ask Dr. Edwards from the telephone to
5 weigh in with her question?

6 DR. EDWARDS: My question was about,
7 stepping back, when we look at adverse events, we
8 want to see if the biologic basis for them is
9 reasonable, and we've seen the literature that was
10 sent about inhibition of sclerostin, possibility of
11 calcification.

12 In the past, drugs used for osteoporosis
13 were subjected to carcinogenicity studies, given
14 that they were going to be chronic medication, and
15 preclinical studies, usually murine models, were
16 done in which the drug was given at high doses for
17 prolonged periods of time.

18 Does Amgen have those studies? Since it can
19 let us know some degree of severity. Risk factors
20 for coronary disease are so prevalent in our
21 population that these findings on a clinical trial
22 can really be magnified enormously in the

1 community. How severe is this effect?

2 DR. WASSERMAN: I'm going to call Dr. Boyce
3 to discuss our preclinical toxicology package. I
4 would stress, though, that what we're looking at
5 here is there's this question; there's uncertainty
6 with the cardiovascular risk.

7 We did extensive work preclinically to try
8 to address it, as Dr. Edwards alluded to, to
9 elucidate whether there was a biological basis for
10 this.

11 Dr. Boyce?

12 DR. BOYCE: Rogely Boyce, nonclinical. Yes,
13 in summary, we conducted a very comprehensive
14 nonclinical package that consisted of a complete
15 toxicology package that met ICH guidelines for
16 biologics. It also included a carcinogenicity
17 study. We also conducted additional cardiovascular
18 studies in ApoE knockout mice and some other
19 additional studies that are summarized in the
20 briefing document, as well as review of the
21 literature.

22 The totality of that data supports that we

1 were unable to identify a biologically plausible
2 mechanism for a causal relationship of romo with MI
3 and stroke. In conducting those studies, we were
4 very mindful of what had been proposed to be
5 functions of sclerostin being inhibitor of vascular
6 calcification as well as inhibitor of athero and
7 systemic inflammation.

8 DR. EDWARDS: Okay. Thank you.

9 DR. LEWIS: Thank you. Dr. Braunstein, and
10 then Dr. Adler?

11 DR. BRAUNSTEIN: Braunstein. On slide CV-19
12 and in the briefing book, you mentioned study 174,
13 which was carried out in males, but it also had an
14 imbalance in the cardiovascular events. I wonder
15 if you can describe that in a little bit more
16 detail and tell us what that imbalance was due to
17 or what the numbers looked like and how you
18 analyzed it.

19 DR. WASSERMAN: Sure. Study 174, as I
20 noted, was conducted in 245 men with osteoporosis.
21 It was a 2 to 1 randomization, so for every 2
22 subjects that received romo, 1 received a placebo.

1 In total, there were 10 subjects with 11 positively
2 adjudicated events, of which there was 1 myocardial
3 infarction, a total of 4 strokes, and 3 patients
4 that had cardiovascular death over that 12-month
5 period.

6 Slide up. Just in an attempt to allay any
7 concerns around this, this is a time to first MACE
8 at 12 months. You can see the number of events
9 here in the time to first event is a total of 8,
10 obviously very wide confidence intervals. It does
11 not affect the meta-analysis or the challenge that
12 we have today.

13 In general -- and I can ask Dr. Sabatine to
14 comment -- this number of events is too small to
15 come up with any conclusions.

16 Dr. Sabatine?

17 DR. SABATINE: Sure. I can just add that in
18 the realm of cardiovascular trials, 8 events is
19 what we would accrue in 1 week for one of our
20 cardiovascular trials, where typically we're
21 targeting a thousand, 1500 events.

22 We would be very loathed to draw any

1 conclusions from 8 events, and even be hesitant to
2 draw conclusions from even the 60 events, which is
3 why I think it's helpful to try to put together the
4 totality of the data to get a better sense of
5 whether there is even any signal.

6 DR. LEWIS: Thank you. Dr. Adler?

7 DR. ADLER: Robert Adler. For the
8 postmarketing surveillance trial, what type of
9 clinician do you expect will be prescribing romo?

10 DR. WASSERMAN: Dr. Cosman, can I ask you to
11 come up as a clinician and help us and Dr. Adler
12 understand where you think who will be prescribing?

13 DR. COSMAN: I think, largely, this is going
14 to be people who have a particular interest in
15 osteoporosis, which could be, of course,
16 endocrinologists like us, rheumatologists, but
17 internists with a particular interest, some
18 gynecologists, and perhaps some orthopedists would
19 also be people who I would expect in the initial
20 phase, and then maybe down the line, some
21 liberalization of that.

22 But I think, initially, it would be people

1 who are more familiar with what is really important
2 in the osteoporosis field, who are the highest risk
3 patients and who is most likely to before.

4 DR. LEWIS: Thank you. Dr. Khosla, then
5 Dr. Burman, and then we'll be taking a break.

6 DR. KHOSLA: This is just to follow up on
7 the issue of biologic plausibility. There is a
8 mention made about the genetic syndromes of
9 sclerostin deficiency, and maybe if one of the
10 Amgen team could expand on that.

11 How many subjects have been looked at? Is
12 it anecdotal that they don't have cardiovascular
13 disease or has there been some kind of rigorous
14 analysis of those families? And what kind of
15 effect size would that analysis exclude? Because
16 that would be the most experiment of nature that
17 would provide insight into this.

18 DR. WASSERMAN: Yes. Thanks, Dr. Khosla.
19 It's a very good question. We've done these
20 analyses both through, like, UK Biobank, as well as
21 partnering with our colleagues at D-Code. They did
22 an extensive analysis and looked at this.

1 Off the top of my head, I can't recall the
2 actual numbers. I'll see if I can get that to you.

3 DR. LEWIS: Thank you. Dr. Burman?

4 DR. BURMAN: Thank you. I was just going to
5 ask the same question Dr. Khosla asked. Thank you.

6 DR. LEWIS: Thank you.

7 I know there are some people who have second
8 or third questions, and I'm going to ask them to
9 please hold on to those questions. We may get some
10 additional time for questions, clarifying questions
11 later, and definitely for discussion. I have to
12 remind folks that sometimes questions are more
13 rebuttal, and discussion, we want to reserve time
14 for everybody to weigh in.

15 At this time, we are going to take a break.
16 I think we only have time for 11 minutes at this
17 point. I'd ask the panel members to please
18 remember not to discuss any of the meeting topics
19 during the break, amongst yourselves, or with any
20 member of the audience, and we resume at 10:40.
21 Thank you.

22 (Whereupon, at 10:30 a.m., a recess was

1 taken.)

2 DR. LEWIS: Thank you. I'd like to now ask
3 the FDA to proceed with their presentations.

4 **FDA Presentation - Jacqueline Karp**

5 DR. KARP: I'm Jacqueline Karp, the clinical
6 reviewer for this application. My presentation
7 will summarize the key efficacy and safety findings
8 of romosozumab as derived from trial 337 and trial
9 142, the two fracture trials in women with
10 postmenopausal osteoporosis. I will also discuss
11 the cardiovascular safety concern raised by the
12 findings of trial 142.

13 As we've heard, romosozumab is a monoclonal
14 antibody that binds to and inhibits sclerostin.
15 Sclerostin, a glycoprotein secreted by osteocytes,
16 targets osteoclast receptors to inhibit bone
17 formation and also increases bone resorption via
18 effects on osteoclast mediators. By inhibiting
19 sclerostin, romosozumab both increases bone
20 formation and decreases bone resorption.

21 This table summarizes the two fracture
22 trials, which were both conducted in a population

1 of women with postmenopausal osteoporosis.
2 Compared to trial 337, trial 142 had a population
3 at higher fracture risk, as all subjects were
4 required to have a history of fragility fracture.

5 In trial 337, subjects were randomized
6 1 to 1 to receive either romosozumab or placebo for
7 12 months. All subjects then received follow-on
8 therapy with denosumab for 12 months. The primary
9 endpoints were subject incidence of morphometric or
10 radiographic vertebral fracture at month 12 and at
11 month 24. Morphometric included both symptomatic
12 and asymptomatic vertebral fractures.

13 In trial 142, subjects were randomized
14 1 to 1 to receive either romosozumab or the active
15 control, alendronate, for 12 months. All subjects
16 then received follow-on therapy with alendronate
17 through the end of the trial.

18 This duration varied for each subject as the
19 trial was event driven. The primary endpoints were
20 subject incidence of morphometric vertebral
21 fracture at month 24 and clinical fracture at the
22 primary analysis. Clinical fracture was defined as

1 symptomatic vertebral fracture or non-vertebral
2 fracture. The primary analysis occurred when at
3 least 333 subjects had a clinical fracture and all
4 subjects completed the 24-month visit.

5 In trial 337, the placebo-controlled trial,
6 both primary endpoints were met. The absolute risk
7 reduction for vertebral fractures was 1.3 percent
8 at month 12 for romosozumab compared to placebo and
9 1.9 percent at month 24 for romosozumab followed by
10 denosumab compared to placebo followed by
11 denosumab, with corresponding relative risk
12 reductions of 73 percent and 75 percent.

13 The first secondary endpoint in the
14 sequential testing in trial 337 was also met. For
15 clinical fracture at month 12, romosozumab
16 demonstrated an absolute risk reduction of
17 1.2 percent and a relative risk reduction of
18 36 percent compared to placebo.

19 Although almost 90 percent of the clinical
20 fractures at 12 months were non-vertebral
21 fractures, the reduction in non-vertebral fractures
22 was not significant and testing was subsequently

1 stopped.

2 Trial 337 was not powered to assess hip
3 fractures, a subset of non-vertebral fractures.
4 However, hip fracture endpoint results are included
5 for consideration since hip fractures are
6 associated with the highest morbidity and mortality
7 of all fractures.

8 Romosozumab significantly increased bone
9 mineral density, or BMD, at all sites assessed. At
10 month 12, compared with placebo, romosozumab
11 increased BMD by 12.7 percent at the lumbar spine,
12 5.8 percent at the total hip, and 5.2 percent at
13 the femoral neck. Romosozumab followed by
14 denosumab maintained significant increases in BMD
15 at all sites at month 24.

16 In trial 142, the active controlled trial,
17 both primary endpoints were met. For vertebral
18 fractures at month 24, the absolute risk reduction
19 was 4 percent and the relative risk reduction
20 50 percent for romosozumab followed by alendronate
21 compared to alendronate alone.

22 For the event-driven clinical fracture

1 endpoint, a stratified Cox proportional hazards
2 model was used for analysis. Through the primary
3 analysis period, which had a median follow-up of
4 33 months, the hazard ratio for clinical fracture
5 was 0.73 for romosozumab followed by alendronate
6 compared to alendronate alone based on 464 subjects
7 with a clinical fracture.

8 In the hierarchy of secondary endpoints, BMD
9 endpoints were tested first, which I will discuss
10 in the next slide. Non-vertebral fracture was
11 evaluated after BMD. Through the primary analysis
12 period, the hazard ratio for non-vertebral
13 fractures was 0.81 for romosozumab followed by
14 alendronate compared to alendronate alone, based on
15 395 subjects with a non-vertebral fracture.

16 Through the primary analysis period, the
17 hazard ratio for hip fracture was 0.62 for
18 romosozumab followed by alendronate compared to
19 alendronate alone based on 107 subjects with hip
20 fracture.

21 This endpoint was not part of the planned
22 testing sequence, and as with trial 337, trial 142

1 was not powered to assess hip fracture. However,
2 this result is included for consideration, again,
3 since hip fractures have the most serious clinical
4 consequences.

5 Significantly higher BMD increases were
6 observed with romosozumab compared to alendronate
7 at all sites assessed. The increase was
8 8.7 percent higher at the lumbar spine, 3.3 percent
9 at the total hip, and 3.2 percent at the femoral
10 neck. Romosozumab followed by alendronate
11 maintained the significantly higher increases in
12 BMD at all sites at month 24.

13 In summary, trial 337 demonstrated
14 romosozumab's benefit of reducing vertebral
15 fractures as early as 12 months, a benefit that
16 persisted through month 24 with 12 months of
17 follow-on denosumab therapy.

18 Trial 142 demonstrated a superiority of
19 romosozumab followed by alendronate over
20 alendronate alone in reducing vertebral, clinical,
21 and non-vertebral fractures. Romosozumab also
22 demonstrated significantly higher BMD increases at

1 the lumbar spine, total hip, and femoral neck
2 compared to both placebo and alendronate.

3 I will now discuss the safety of
4 romosozumab, which is predominantly derived from
5 the 12-month double-blind treatment periods in
6 trials 337 and 142. All results discussed in this
7 section are for the 12-month double-blind periods
8 of the trials.

9 As outlined in this table, the rates of
10 overall adverse events and types of adverse events
11 were similar between trials, and between treatment
12 groups within each trial, with the exception of a
13 higher incidence of serious adverse events in
14 trial 142 compared to trial 337.

15 Overall, types of fatal events were balanced
16 between treatment groups in both trials with two
17 notable exceptions. In trial 337, there was an
18 imbalance in deaths due to neoplasms, which
19 occurred in 3 placebo-treated subjects and in
20 8 romosozumab-treated subjects. This imbalance was
21 due to malignant lung neoplasm events, which
22 occurred in no placebo-treated subjects and in

1 4 romosozumab-treated subjects.

2 All subjects were current or former smokers
3 and all had a short time to diagnosis. And of
4 note, the overall incidence of fatal and nonfatal
5 lung neoplasm events was balanced between treatment
6 groups.

7 The other imbalance, which was observed in
8 trial 142, was in deaths due to cardiac disorders,
9 which occurred in 3 alendronate-treated subjects
10 and in 9 romosozumab-treated subjects. Cardiac
11 disorders will be discussed further in later
12 sections of our presentation.

13 The incidence of all serious adverse events
14 was balanced between treatment groups within each
15 trial, although overall, this incidence was higher
16 in trial 142 compared to trial 337. The types of
17 serious adverse events were balanced between
18 treatment groups within each trial, with one
19 notable exception observed in trial 142.

20 This was a higher incidence of positively
21 adjudicated cardiovascular serious adverse events
22 in romosozumab-treated subjects versus alendronate-

1 treated subjects. These events will be discussed
2 further in later sections of our presentation.

3 The following events were considered events
4 of interest based on prior reports of such events
5 with other therapies that inhibit bone resorption
6 or with other injected therapeutic proteins.
7 Adverse events of hypocalcemia were very rare in
8 both trials and none were considered serious.

9 Mild decreases in serum calcium occurred
10 with romosozumab with the nadir occurring at
11 month 1 and normalization occurring by month 12 in
12 both trials. The lowest reported value was grade 2
13 in severity.

14 The incidence of injection site reactions
15 was slightly higher in romosozumab-treated subjects
16 in both trials. None were reported as serious.
17 The most common preferred terms were injection site
18 pain and injection site erythema.

19 Potential hypersensitivity reactions were
20 balanced between treatment groups in both trials,
21 although events considered serious were slightly
22 higher in romosozumab-treated subjects. For the

1 more concerning of these events, such as ITP,
2 circulatory collapse, angioedema, and exfoliative
3 dermatitis, there were factors to explain a cause
4 other than romosozumab.

5 Atypical femoral fractures and osteonecrosis
6 of the jaw were also adverse events of interest.
7 All potential cases were adjudicated by an
8 independent committee. In trial 337, there was one
9 positively adjudicated case of each of these
10 events, both in romosozumab-treated subjects. In
11 trial 142, there were no cases of either of these
12 events. The occurrence of these events was not
13 anticipated with romosozumab, given its
14 predominantly anabolic action.

15 Malignant or unspecified tumors were
16 considered events of interest due to the presence
17 of a common pathway that plays a role in both
18 sclerostin signaling and some tumor suppressor
19 signaling. Given the overall balanced incidence of
20 these events between treatment groups throughout
21 the two trials, as well as the confounding factors
22 in the fatal neoplasm events in trial 337

1 previously discussed, the totality of data does not
2 suggest a safety signal for neoplasms. However,
3 since these data are for only 1 year of therapy,
4 conclusions regarding potential carcinogenicity
5 cannot be made.

6 There were no major safety concerns
7 regarding immunogenicity. Of romosozumab-treated
8 subjects with post-baseline results for anti-drug
9 antibodies, or ADAs, 18 percent tested positive in
10 trial 337 and 15 percent tested positive in
11 trial 142. Of these ADAs, very small percentages
12 were neutralizing. Serum romosozumab
13 concentrations decreased slightly in ADA-positive
14 subjects compared to ADA-negative subjects.
15 However, ADAs had no effect on efficacy or safety
16 parameters.

17 Given these safety findings, our only major
18 concern is romosozumab's cardiovascular safety, and
19 I will now turn our attention to this matter. The
20 adjudication of potential cardiovascular serious
21 adverse events was prespecified in the trial
22 protocols. This was performed by the Duke Clinical

1 Research Institute or DCRI.

2 This adjudication included all deaths, all
3 serious adverse events meeting prespecified trigger
4 terms, and additional serious adverse events
5 identified by DCRI during review of triggered
6 events. Investigators also had the option to flag
7 potential cardiovascular serious adverse events for
8 adjudication.

9 As listed in this table, there was an
10 imbalance in positively adjudicated cardiovascular
11 serious adverse events in the 12-month double-blind
12 treatment period in trial 142 with an incidence of
13 1.9 percent in alendronate-treated subjects versus
14 2.5 percent of romosozumab-treated subjects.

15 This imbalance was driven by cardiac
16 ischemic events, which were mostly myocardial
17 infarction events, and cerebrovascular events,
18 which were mostly stroke events, and to a lesser
19 extent, cardiovascular deaths. In contrast, these
20 events were all balanced between treatment groups
21 in trial 337.

22 To further explore this safety signal that

1 arose in trial 142 and the divergent results
2 between the trials, the applicant performed
3 additional measures to evaluate cardiovascular
4 safety. These measures included a readjudication
5 of all events previously adjudicated by DCRI,
6 performed by the thrombolysis and myocardial
7 infarction or TIMI study group.

8 The TIMI study group also performed a post
9 hoc review of all adverse event data with
10 adjudication of all potential cardiovascular
11 adverse events, both serious and non-serious.

12 Colleagues from the Division of
13 Cardiovascular and Renal Products reviewed the DCRI
14 and TIMI adjudication procedures and confirmed that
15 their results were similar. Our assessment focuses
16 on the DCRI results.

17 Although the prespecified endpoint for the
18 adjudication was the incidence of cardiovascular
19 serious adverse events, it is important to
20 understand the risk in terms of the impact on the
21 major adverse cardiac event or MACE composite
22 endpoint, which is comprised of cardiovascular

1 death, nonfatal myocardial infarction, or nonfatal
2 stroke. An ad hoc analysis of the MACE endpoint
3 was thus performed.

4 As listed in this table, this analysis
5 showed an imbalance in a subject incidence of MACE
6 during the 12-month double-blind period in
7 trial 142, occurring in 1.1 percent of alendronate-
8 treated subjects versus 2 percent of romosozumab-
9 treated subjects. There was no imbalance in MACE
10 in trial 337.

11 This table also lists the results for the
12 individual components of the MACE composite. As
13 you can see, the incidence of each component was
14 higher in romosozumab versus alendronate-treated
15 subjects in trial 142 and balanced between
16 treatment groups in trial 337.

17 For the overall study periods, the subject
18 incidence of MACE was balanced between treatment
19 groups in both trials. The individual components
20 of MACE were also balanced, with the exception of
21 stroke events in trial 142, which had a higher
22 incidence in subjects who initially received

1 romosozumab versus alendronate.

2 These Kaplan-Meier plots depict the time to
3 first MACE in trials 337 and 142, the one on the
4 left for the 12-month double-blind period and the
5 one on the right for the overall study period. The
6 red lines represent trial 337 and the black lines
7 trial 142. Solid lines represent romosozumab arms
8 and dashed lines represent placebo or alendronate
9 arms for trial 337 or 142, respectively.

10 The tables at the bottom list the number of
11 subjects at risk at certain time points for each
12 treatment arm, listed in the same order as the arms
13 in the legends at the top. As seen in the figures,
14 there is an early separation of the trial 142 arms
15 from each other, reflecting the higher incidence of
16 MACE events that occurred in romosozumab-treated
17 subjects versus alendronate-treated subjects early
18 in the trial. Of note, after several months, the
19 separation does not continue to widen.

20 I will now turn the discussion over to my
21 colleague, Dr. Jung, who will discuss the
22 statistical analysis of the cardiovascular safety

1 results.

2 **FDA Presentation - Hyun Jung**

3 DR. JUNG: Good morning. I'm Tae Hyun Jung,
4 a statistical reviewer from the Office of
5 Biostatistics, and I will present FDA's
6 cardiovascular safety assessment from a statistical
7 perspective.

8 The FDA's cardiovascular assessment compares
9 the CV risk in romosozumab versus comparator in
10 women with postmenopausal osteoporosis. Two women
11 trials of study 337 and study 142 compared
12 romosozumab to different comparators, placebo and
13 alendronate, respectively.

14 The objective of this assessment is to
15 explore a scientific finding across these trials.
16 Traditional meta-analysis combines evidence from
17 relevant studies using appropriate statistical
18 methods to make inference on the population of
19 interest. However, the inference using this method
20 in romosozumab trials could be limited because it
21 considers alendronate and placebo-treated as one
22 comparator. Therefore, it did not distinguish the

1 effect of the active control, alendronate, on CV
2 risk from the placebo effect, nor does it compare
3 alendronate and placebo.

4 Therefore, the FDA conducted a network
5 meta-analysis, which is an extension of the
6 traditional meta-analyses. Network estimates are
7 weighted sums of the observed estimates and
8 compares multiple treatment simultaneously by using
9 direct and indirect evidence within a network of
10 randomized clinical trials.

11 The network meta-analysis preserved
12 within-trial randomized comparison of each study
13 and enables indirect comparisons of multiple
14 interventions that have not been studied in
15 head-to-head trials, so alendronate versus placebo
16 can be explored in the two women trials.

17 In the network meta-analysis, we assumed
18 there are no effect modifiers. What this means is
19 that the effect of the drug does not vary by
20 difference into population among the trials.

21 When the comparators of the studies are the
22 same, for example using drug A with the same

1 comparator, drug B, the estimates from the
2 meta-analysis and the network meta-analysis are the
3 same. When other comparators, drug C, D, and E,
4 are compared to drug A in different studies, the
5 meta-analysis consider all these different
6 comparators as one single comparator, while the
7 network meta-analysis maps these unique comparators
8 distinctively with the common comparator, drug A.

9 So based on these different studies, the
10 meta-analysis estimates an overall treatment effect
11 as a weighted average of these individual studies.
12 In network meta-analysis, the direct effects are
13 estimated from studies directly randomizing
14 treatment of interest, and the indirect effects are
15 estimated from studies comparing treatment of
16 interest with the common comparator.

17 In detail, the indirect effect is estimated
18 using separate comparison of two interventions,
19 that is, romosozumab versus alendronate from study
20 142, romosozumab versus placebo from study 337, and
21 takes into account a common comparator, that is
22 romosozumab. Thus, the direct treatment effects of

1 each intervention against a common comparator are
2 used to estimate on indirect evidence between the
3 two interventions.

4 The indirect effect is estimated by the
5 following steps. The first step is to estimate the
6 direct effect of each study in study 142 and
7 study 337. The hazard ratio of MACE is 1.87 and
8 1.03, respectively.

9 The next step is to transform these direct
10 effects using the romosozumab as a denominator. So
11 inversing the hazard ratio leads to alendronate
12 over romosozumab and placebo over romosozumab. The
13 hazard ratios are equivalent to the exponentiated
14 log hazard ratios.

15 Step 3 is subtracting the log hazard ratios
16 from each study with weights. Thus, the indirect
17 estimate is roughly the difference between the
18 2 bars from the figure below.

19 In the network meta-analysis, we conducted
20 analysis using the fixed-effect model. The
21 fixed-effect model produced a valid estimate, and
22 with only two trials, other models are not

1 feasible. The primary safety outcome are
2 DCRI-adjudicated MACE events. Our analysis
3 population is a safety population, which includes
4 all randomized subjects who receive at least
5 1 active dose of either romosozumab, placebo, and
6 alendronate in the 12-month double-blind study
7 period. In analysis, we did not adjust the alpha
8 level or type 1 error for multiple testing.

9 The analysis results are summarized in the
10 tables. All results are estimated based on the
11 first year of the double-blind study period.

12 First, with the Cox regression analysis, in
13 study 337, the hazard ratio with the 95 percent
14 confidence interval of MACE, comparing romosozumab
15 to placebo, was 1.03 with the confidence interval
16 between 0.62 and 1.72, indicating no difference in
17 risk.

18 The individual components of MACE, that is,
19 CV death, nonfatal myocardial infarction, nonfatal
20 stroke, are present at below the MACE endpoint.

21 For each component, the risk was not different
22 between the treatment arms. However, in study 142,

1 the hazard ratio of MACE comparing romosozumab to
2 alendronate was 1.87 with a 95 percent confidence
3 interval between 1.11 and 3.14, indicating a higher
4 risk in the romosozumab arm.

5 In the individual components of MACE, all
6 components show a hazard ratio greater than 1. The
7 hazard ratio of nonfatal myocardial infarction was
8 3.2 with a confidence interval that did not include
9 1.

10 The meta-analysis result that does not
11 distinguish alendronate and placebo yields a hazard
12 ratio of 1.38 with a 95 percent confidence interval
13 between 0.96 and 1.99. In the network
14 meta-analysis, the direct estimate of romosozumab
15 versus placebo yielded hazard ratio of 1.03 with a
16 confidence interval between 0.62 and 1.72. The
17 hazard ratio was the same as that of the study 337
18 because only the study compared romosozumab and
19 placebo.

20 In contrast, the indirect estimate of the
21 hazard ratio comparing alendronate to placebo was -
22 0.55 with a 95 percent confidence interval between

1 0.27 and 1.14. Although the confidence interval
2 included 1, the risk of MACE in alendronate was
3 lower compared to the placebo.

4 Now the summary; in study 142, the risk of
5 MACE was higher with romosozumab than alendronate
6 in that double-blind period, while study 337
7 presented no different risk of MACE between
8 romosozumab and placebo group. Inference about the
9 hazard ratio of MACE in the meta-analysis was
10 limited by treating alendronate and placebo as a
11 single comparator.

12 The FDA used network meta-analysis to
13 differentiate alendronate effect and placebo effect
14 and explore the indirect effect of alendronate
15 versus placebo.

16 As mentioned by Dr. Karp, study 142 included
17 subjects with higher risk of fracture against
18 study 337. If there are effect modifiers related
19 to the difference in the populations, this may
20 explain the difference in results between the
21 trials. In addition, inference is limited by using
22 only two studies, which limits the ability to

1 examine the reasons for the difference in the
2 results. Because the study was not powered on
3 MACE, analyses were post hoc and exploratory.

4 In conclusion, the estimated hazard of MACE
5 was highest in the romosozumab group and lowest in
6 the alendronate group. It is difficult to discern,
7 based on this analysis, whether the increased risk
8 of MACE identified in the romosozumab group in
9 study 142 is truly a drug effect, chance finding,
10 or because of the reduced risk of MACE in the
11 alendronate group.

12 This is the end of my presentation, and
13 next, Dr. Kehoe will talk about cardiovascular
14 safety summary.

15 **FDA Presentation - Theresa Kehoe**

16 DR. KEHOE: Good morning. I'm Theresa
17 Kehoe, the cross-discipline team leader for this
18 application, and I'm going to be talking mostly
19 about the cardiovascular summary and then also the
20 risk-benefit.

21 As we've just heard in the osteoporosis
22 fracture trials, 142 and 337, the hazard ratio for

1 MACE approached 2. This leads us to think about
2 what is the plausibility of this. Certainly, we've
3 seen research in recent years looking at bone
4 targets and diabetes metabolic syndrome and
5 associated cardiovascular disease, but at this
6 point, there is little data available on the
7 interplay of sclerostin and the cardiovascular
8 disease or cardiovascular risk factors.

9 We do know that sclerostin is expressed in
10 the aorta and in vascular and valvular
11 calcifications, but we do not know the role of
12 sclerostin there. We also see in rare diseases,
13 where the sclerostin is underexpressed or absent,
14 such as Van Buchem's disease or sclerosteosis,
15 patients do not appear to have an increased risk of
16 cardiac disease.

17 So when we look at the trials separately, we
18 see conflicting results. In trial 337, the hazard
19 ratio was 1.03 compared to trial 142, where the
20 hazard ratio was 1.87. That leads us to consider
21 whether there are differences between these two
22 trials that could explain this.

1 We started by looking at the baseline
2 osteoporosis characteristics, and if you recall
3 from Dr. McClung's talk earlier, the T-score of
4 minus 2.5 is what is used for bone density to
5 diagnose osteoporosis.

6 Here in this slide, we can see that between
7 these two trials, patients in trial 142 were
8 slightly older with a mean age of 74 years as
9 opposed to 71 years in 337. We also see that for
10 lumbar spine and total hip, bone mineral density
11 was lower in trial 142 when compared to 337.

12 The main difference between these two
13 trials, however, was the prevalent fracture, the
14 risk for fracture, patients who had a fracture at
15 baseline. These occurred in 96 percent of patients
16 enrolled in trial 142 and 18 percent of patients in
17 trial 337.

18 We started to look at the MACE
19 characteristics based on the osteoporosis at
20 baseline, and here is the breakdown by age. What
21 you can see is -- this is in trial 142 -- in
22 patients greater than 75 years of age, the hazard

1 ratio does not cross 1. It's 1.93. Age less than
2 75 years, the hazard ratio was 1.76, but it does
3 cross 1 because we're getting into smaller events.
4 At age less than 65, the hazard ratio was 3, but
5 again, with a very wide confidence interval because
6 of the small number of events. When we look at
7 trial 337, we don't see a similar pattern.

8 We took a look at lumbar spine T-score, and
9 actually, the hazard ratio for patients who had a
10 T-score better than minus 3 did not cross 1 with a
11 hazard ratio of 2.56. Compared to patients with a
12 lower lumbar spine T-score, the hazard ratio was
13 1.35. Again, they are not similar patterns seen in
14 trial 337.

15 Then we look specifically at cardiovascular
16 risk and the risk characteristics, and there are
17 only a slightly increased number of patients with
18 any cardiovascular-related disease, 79 percent in
19 trial 142 versus 75 percent in trial 337.

20 As we look at the various diseases, there
21 are small differences in all the various
22 categories, most notably in cardiovascular disease

1 and hypertension. Conversely, hyperlipidemia was
2 the baseline diagnosis in patients enrolled in
3 trial 337 with 39 percent versus 34 percent for
4 trial 142.

5 Unfortunately, baseline lipid levels were
6 not checked as part of the baseline
7 characteristics, so we really don't know what the
8 lipid levels for these patients were.

9 When we look at the MACE subgroup analysis
10 based on baseline cardiovascular risks as any
11 cardiovascular risk factor at baseline versus no
12 cardiovascular risk factor at baseline, we can see
13 that in trial 142, the hazard ratio does not cross
14 1 with a hazard ratio of 2.07. In patients with no
15 cardiovascular risk factors, the hazard ratio is
16 0.49, but it's a wide confidence interval because
17 the event rate is small. Again, we do not see a
18 similar pattern in trial 337.

19 Our subgroup analysis, what we can
20 determine, is that we don't see population
21 differences between these two studies that could
22 explain the trial differences that we see, and that

1 leads to the final difference, which is the
2 comparator.

3 In trial 337, the comparator was placebo,
4 and in trial 142, the comparator was alendronate.
5 This leads to the question, is there cardiovascular
6 protection with alendronate use? Certainly, there
7 is potential biologic plausibility. Both the
8 bisphosphonates and the statins act along the
9 methylenate pathway.

10 However, alendronate has a very high
11 specificity to bone and low systemic exposure, and
12 the study results to date looking at this question
13 have been very mixed. We did go back to the
14 original fracture trials with alendronate versus
15 placebo, and there was no evidence of
16 cardiovascular benefit.

17 So that brings us to this slide, which is
18 the Kaplan-Meier curve, and again, what has been
19 pointed out is the early separation in this curve.
20 And that leads to the question, is there something
21 happening early in the romosozumab exposure that
22 could explain this such as changes in blood

1 pressure, looking at vasoconstriction, or platelet
2 aggregation?

3 We asked for these analyses from Amgen after
4 our first review cycle, and they provided the data
5 and did further evaluations on this. For blood
6 pressure, there was no effect on systolic or
7 diastolic blood pressure evaluated at months 1, 6,
8 and 12 in the fracture trials. Ambulatory blood
9 pressure was not conducted and further blood
10 pressure analyses are not possible.

11 For an effect on vasoconstriction, it was an
12 in vitro study using human coronary artery rings,
13 and there was no effect on vascular tone in this
14 study.

15 To look at platelet aggregation, an in vitro
16 study in platelet activation was conducted, and
17 there was no effect on platelet activation at
18 concentrations up to 10 times the intended human
19 dose.

20 So what we are left with is 1 of 2 large
21 safety and efficacy trials of romosozumab for the
22 treatment of osteoporosis in postmenopausal women

1 that has yielded a concerning safety signal. We
2 know that SOST is expressed in the cardiovascular
3 system, however, the nonclinical studies do not
4 provide support for an association. There are a
5 small number of MACE in both trials, making
6 subgroup analyses difficult, and it is not clear
7 that the population differences between the two
8 trials can explain the results.

9 Then we look at romosozumab benefit and
10 risk. The benefit is the fracture risk reduction.
11 We know that there is morbidity and mortality
12 associated with fracture, most notably hip
13 fractures. Osteoporosis and fracture risk increase
14 in women after menopause, and romosozumab is
15 efficacious in preventing fractures.

16 The risk is the cardiovascular safety. We
17 know that there is morbidity and mortality
18 associated with ischemic cardiovascular and
19 cerebrovascular events. Cardiovascular disease is
20 the leading cause of death in women, and
21 cardiovascular risk increases in women after
22 menopause. So the question remains, does

1 romosozumab cause an increased risk for adverse
2 cardiovascular outcomes?

3 Then we looked at the risk-benefit in a
4 slightly different model using the incidence rates
5 of fractures for each of these trials. We do
6 recognize that non-vertebral and hip fractures were
7 not necessarily considered in the statistical
8 analyses or that they met the statistical
9 significance. However, in this situation, we felt
10 it important to include them because that is where
11 the morbidity and mortality is more so than in
12 morphometric vertebral fractures, which are
13 predominantly radiographic asymptomatic findings.

14 In looking at this table with trial 337, if
15 a thousand women are treated with romosozumab for a
16 year compared to placebo, we would expect 13 fewer
17 women to have a new morphometric vertebral fracture
18 at 1 year; 8 less women having non-vertebral
19 fracture at 1 year; and 3 fewer women having hip
20 fracture at 1 year; and we would expect no
21 difference in the MACE events.

22 When we look at trial 142, a group of

1 patients that clearly are at higher fracture risk
2 versus alendronate, 1,000 women treated with
3 romosozumab, we would expect to see 18 fewer women
4 with morphometric vertebral fracture; 14 fewer
5 women with non-vertebral fracture; and 3 fewer
6 women with hip fracture. However, we would expect,
7 based on this study, to see 9 more MACE events in
8 women.

9 So what are the next steps? This is why
10 we've asked you here today, to discuss what the
11 next steps are, and that is for the further
12 evaluation of the cardiovascular signal; the type
13 of trial or study that would need to be done,
14 either a cardiovascular outcomes trial or an
15 observational study; and also the timing of that
16 trial or study pre-approval or post-approval.

17 When we talk about cardiovascular outcomes
18 trials -- these are prospective randomized
19 controlled trials -- the challenges are they must
20 have a large sample size. There are difficulties
21 with follow-up and missing data is a challenge, and
22 also the question of whether they are generalizable

1 to the entire study population since most patients
2 who are enrolled in these trials are at high risk
3 for cardiovascular events.

4 The additional challenge with romosozumab is
5 that it's a 1-year duration of therapy. However,
6 the orderly separation of the Kaplan-Meier curves
7 in trial 142 may indicate that a 1-year duration
8 may be sufficient.

9 I'm going to now turn the podium over to
10 Dr. Liu, who will discuss the feasibility of
11 observational trials.

12 **FDA Presentation - Wei Liu**

13 DR. LIU: Good morning, everyone. I'm Wei
14 Liu from the Division of Epidemiology II in the
15 Office of Surveillance and Epidemiology. I'll be
16 discussing the feasibility of using observational
17 data to assess the cardiovascular risk associated
18 with romosozumab.

19 Here is an outline of my talk, starting with
20 a summary of the regulatory context for
21 postmarketing safety surveillance, followed by a
22 discussion on possible study design options,

1 including randomized cardiovascular safety outcome
2 trials and observational studies. Then I will
3 discuss the strengths and limitations of using
4 observational database study to evaluate
5 romosozumab cardiovascular safety signal.

6 The FDA monitors medical product safety
7 through a variety of mechanisms. Conducting
8 postmarketing active surveillance is one of them
9 and includes 3 steps.

10 Signal detection is the generation of a
11 hypothesis regarding a signal of a serious risk
12 associated with the drug. Signal refinement is the
13 process to test or refine a hypothesis to narrow
14 uncertainty about a signal. The intent of signal
15 evaluation is to establish or refute causal
16 relationships.

17 The type of study approach needed to support
18 each of these regulatory goals may depend on the
19 original source of the signal, the level of
20 regulatory concern, and the desired precision of
21 the evidence necessary to meet their purpose.

22 In general, the level of evidence needed

1 increases along with an increasing level of
2 regulatory concern, and a higher precision of
3 evidence needed usually means an increasing level
4 of validation to overcome data source limitations
5 and increasing component control to mitigate the
6 probability of bias.

7 The study question we would like to address
8 is where the romosozumab users are at higher risk
9 of cardiovascular events compared to users who
10 received other anti-osteoporosis therapies.

11 Because the cardiovascular signal arises from
12 pivotal studies of romosozumab, we will limit
13 ourselves to two types of study approaches,
14 cardiovascular safety outcome trials and
15 observational studies.

16 Cardiovascular safety outcome trials are
17 prospective randomized controlled studies conducted
18 to rule out an unacceptable cardiovascular risk in
19 pre- or post-approval settings. These trials
20 typically examine the cardiovascular safety of a
21 new drug in comparison to standard of care.

22 Observational studies can be conducted using

1 primary or secondary data. Primary data involves
2 the active collection of new data by investigators
3 from patients or providers and follow-up
4 prospectively to assess the effect of treatment on
5 particular outcomes.

6 Electronic healthcare data are widely used
7 to study drug safety questions in real-world
8 healthcare settings with a large number of
9 patients. The two main types of secondary data are
10 health insurance claims and electronic medical
11 records. Some data sources are considered hybrids
12 of the two and include both administrative claims
13 data with capacity to access medical records.

14 The applicant has proposed to conduct
15 observational studies in administrative claims
16 databases to assess the comparative cardiovascular
17 safety of romosozumab. I will now comment on the
18 use of observational data, focusing on challenges
19 of these types of data to evaluate the signal.

20 Observational studies can be conducted to
21 complement the evidence generated from clinical
22 trials. Ideally, a good observational study should

1 be designed and conducted to resemble the target
2 trial that would answer the same study question.

3 Using observational studies to evaluate the
4 signal, however, may prove challenging because of
5 the methodology for challenges, including
6 confounding by disease severity, residual
7 confounding, selection bias due to post-index
8 region or treatment discontinuation, and
9 measurement bias.

10 In the next few slides, I will discuss how
11 each of these biases may affect, in turn, validity
12 and techniques to address them. First, I will
13 discuss confounding.

14 Patients considered candidates for
15 romosozumab therapy may have previously treated
16 with other osteoporosis agents or are originally at
17 higher risk for fracture. Thus, users of
18 romosozumab and a comparator may be systematically
19 different if history of reference drug use
20 represents different state of disease progression
21 or different treatment option is a proxy for the
22 severity of underlying disease.

1 Severity of bone disease may influence
2 cardiovascular risk. However, severity of disease
3 is difficult to measure, which may result in
4 confounding by disease severity in database studies
5 to evaluate the comparative safety of romosozumab.

6 Observational studies conducted in claims
7 may also be subject to confounding by unmeasured or
8 partially measured covariates such as smoking, body
9 mass index, and socioeconomic status. In addition,
10 patients' cardiovascular risk profile may evolve
11 over the course of follow-up.

12 Hence, cardiovascular risk factors measured
13 at baseline may be less optimal predictors of
14 future cardiovascular risk as follow-up prolongs.
15 This time-varying confounding, however, may affect
16 both observational studies and randomized trial if
17 it is not controlled in the data analysis.

18 In contrast to trials, where comparability
19 between treatment arms are inherently established
20 by randomization, observational studies must rely
21 on design or statistical adjustment techniques to
22 minimize the potential for confounding bias.

1 The new user active comparator design, which
2 identifies treatment initiator following a washout
3 period, is the backbone of the study design for
4 many comparative safety studies. If the study
5 objective is to evaluate comparator safety among
6 patients, switching from antiresorptive agents to
7 one biologic versus another, then a new switcher
8 design may be more appropriate.

9 For romosozumab compared to safety studies,
10 in addition to those conventional confounders such
11 as demographics, lifestyle, and medical factors,
12 additional information regarding the underlying
13 bone disease severity and other time-varying
14 characteristics might be collected and incorporated
15 in the analysis.

16 Additionally, statistical analysis using
17 exposure propensity score, disease risk score, or
18 instrumental variable analysis can help minimize
19 confounding to some extent.

20 Let's now turn to selection bias. Selection
21 bias is related to the selection and retention of
22 patients in the study. When study compared the

1 safety of romosozumab in comparator safety
2 therapies, it's likely that we may encounter
3 situations of post-index treatment switching and
4 discontinuation.

5 Empirical data suggests that overall
6 compliance rate of osteoporosis therapies,
7 particularly with bisphosphonates, are suboptimal
8 due to reasons such as immediate patient-recognized
9 benefits, adverse events, high treatment costs, or
10 inconvenient dosing.

11 In clinical trials, non-compliance is
12 handled by the use of intention-to-treat analysis.
13 In observational studies, the use of intention-to-
14 treat analysis may lead to exposure
15 misclassification if switching, especially due to
16 medical reasons, happens frequently and is
17 associated with the occurrence of the study
18 outcome. These biases, however, may occur in both
19 clinical trials and observational study.

20 Based on current best practices in
21 observational studies, we should use both
22 as-treated and intention-to-treat analyses to

1 account for the suboptimal compliance to
2 osteoporosis drugs after the index prescription.

3 A more complex potential less biased
4 adjustment method, inverse probability of censoring
5 weights, may be used to account for the treatment
6 switching, but these methods rely on the untestable
7 assumption that data available are all baseline and
8 time-dependent covariates that influences the
9 probability of switching and occurrence of
10 cardiovascular events.

11 Exposure misclassification may also occur in
12 observational studies. In claims data, proof of
13 drug dispensing is not proof of drug exposure. In
14 EMRs, it's always a concern when the patients
15 actually fill their prescription and drug received
16 from other healthcare settings may not be captured
17 by the EMR system being used for the study.

18 Outcome and covariance misclassification can
19 affect the internal validity, especially if billing
20 diagnosis and procedure codes have poor validity.

21 In this slide, I'll comment on the validity
22 of using a coding algorithm to identify the CV

1 events in claims data. Due to the serious nature,
2 hospitalization is expected for most nonfatal
3 events, including myocardial infarction, stroke,
4 and heart failure. However, out-of-hospital
5 cardiovascular deaths are usually not captured in
6 most claims data unless the linkage to a state or
7 national death registry has been established.

8 For nonfatal MI or stroke, the validity of
9 claim-based coding algorithms using the ICD-9
10 discharging diagnosis codes or diagnosis-related
11 group codes were evaluated previously in Medicare
12 data, which showed a high positive predictive
13 value, or PPV, of greater than 90 percent.

14 The PPV for composite outcome, including MI,
15 stroke, heart failure, coronary revascularization,
16 and all-cause mortality is greater than 80 percent
17 in Medicare data.

18 To mitigate a measurement bias, especially
19 if claims data are used, only validated coding
20 algorithm with a high PPV and reasonable
21 sensitivity should be used. In case access to
22 electronic medical records are possible, a blinded

1 independent adjudication of all cases identified by
2 coding algorithm should be used. Regardless of
3 which data sources are used, it's always wise to
4 test the robustness of various case definitions in
5 sensitivity analyses.

6 In this slide, I will summarize the main
7 strengths and limitations of observational studies
8 versus randomized trials for assessing the
9 cardiovascular outcome of exposure to romosozumab.

10 Cardiovascular outcome trials with
11 prespecified safety endpoints are the best evidence
12 design. Compared to observational studies, a well-
13 conducted randomized trial improved comparability
14 of treatment groups and provided better adjustment
15 for covariance, including a measure of confounders.

16 Safety endpoints are usually adjudicated in
17 trials by an independent outcome adjudication
18 committee. Due to sample size restrictions, trials
19 may have limited statistical power to evaluate
20 small relative risk. In addition, a randomized
21 controlled trial may not provide information about
22 the risk profile for certain subpopulations due to

1 trial entry criteria.

2 Finally, to improve the data collection for
3 randomized trials comes at the cost of spending
4 more resources. Compared to trials, observational
5 studies represent how the drug is used in the
6 real-world setting, so the findings from
7 observational studies are generalizable to general
8 practice.

9 Healthcare database studies are sometimes
10 preferred because a large sample size enables less
11 expensive studies of smaller relative risks.
12 However, observational data is usually lack
13 important confounders and may not capture out-of-
14 hospital cardiovascular deaths, so confounding bias
15 is not avoidable in observational studies.

16 In summary, a romosozumab cardiovascular
17 safety study will be complicated by issues of
18 confounding and bias. Selection of study design
19 and data sources should be based on the study
20 questions and driven by the required level of
21 evidence to address the specific regulatory need.

22 Both cardiovascular outcome trials and

1 observational studies can be implemented to address
2 the safety concern depending on the level of
3 evidence desired. Whichever methods are chosen,
4 investigators should design and implement studies
5 according to existing best practices.

6 That's all I have about the observational
7 study. Thank you for listening.

8 **Clarifying Questions to FDA**

9 DR. LEWIS: Thank you.

10 At this point, we'd like to open it up for
11 clarifying questions for the FDA. Please remember
12 to state your name for the record before you speak,
13 and please limit it to just one question. We'll
14 try to get you follow-up time when possible. Let's
15 start with Dr. Khosla and then go to Dr. Shaw.

16 DR. KHOSLA: I want to thank the FDA for
17 their presentations. I'd like to ask a very
18 practical question. If the drug is approved with a
19 warning that says use or not to use in patients at
20 high risk for cardiovascular disease, then the
21 question that the postmarketing study would
22 address, I assume, would be that if it's used with

1 those precautions, what is the actual risk of the
2 drug if that practice is followed?

3 That differs from the scientific question of
4 whether there fundamentally is an increase in
5 cardiovascular risk of the drug, and I would argue
6 they're two different questions. And if you really
7 want to address that scientific question, it may be
8 very, very difficult to answer the question.

9 As a clinician, I'm actually more interested
10 in that practical question of if it's used
11 appropriately, is there an increased risk to
12 patients?

13 DR. LEWIS: For FDA, Dr. Joffe?

14 DR. JOFFE: It's Hylton Joffe. Yes. I
15 think there is a tension there because if you want
16 to assess the cardiovascular safety in a
17 cardiovascular outcomes trial, if you don't enrich
18 that trial enough, you're not going to have enough
19 events and you're not going to be able to answer
20 the question.

21 So typically, cardiovascular outcome trials
22 are enriched, but the tension there is are you

1 enriching the trial with patients who shouldn't be
2 getting the drug in clinical practice if you're
3 saying it should be used in the low cardiovascular
4 risk population.

5 So that's the tension, I think one of the
6 factors you all have to consider as you think about
7 how to evaluate the signal further.

8 DR. LEWIS: Thank you. Dr. Shaw and then
9 Dr. Wang.

10 DR. SHAW: Yes. This is a question for
11 Dr. Jung, who had presented the network
12 meta-analysis as a way to provide direct
13 comparisons for two therapies that weren't directly
14 compared in a trial. On slide 11, you talked about
15 how you could get a direct estimate of the
16 alendronate versus placebo and saw this non-
17 significant trend towards the protective effect.

18 So my question is, for this analysis was
19 simply to what effect -- or if you could just
20 clarify to what extent -- the differences in
21 baseline characteristics in these trials. The
22 trial with the placebo arm had somewhat different

1 baseline characteristics than the trial with
2 alendronate, so to what extent this analysis takes
3 that into account.

4 DR. JUNG: Yes. This is Dr. Jung from the
5 Office of Biostatistics. So we conducted the
6 network meta-analysis to separate out the placebo
7 effect and the alendronate effect instead of
8 combining those two components. And if there are
9 effect modifiers -- so we are not sure what's the
10 effect modifier.

11 I'll say the higher risk of fracture could
12 be a potential modifier, and if the distribution of
13 the effect modifiers are imbalanced between the two
14 women populations, actually, there is a limitation
15 for the inference on the network meta-analysis.

16 So if two populations are pretty similar, we
17 can get a valid estimate using the indirect effect,
18 but if the two populations are heterogeneous, that
19 actually violates the two base assumptions for the
20 network meta-analysis.

21 I'll say the first base assumption for the
22 network meta-analysis is the transitivity; in other

1 words, it's a similarity. So as I said, it's how
2 homogeneous between the two populations.

3 The other one is the consistency, that the
4 indirect effects are consistent with that of the
5 direct effects. And that's an agreement between
6 the direct and indirect evidence for a given pair
7 of treatments.

8 If there had been a trial between
9 alendronate versus placebo, how close is this
10 estimate compared to the indirect effect? So these
11 two assumptions should be maintained if we want to
12 get a valid estimate for the network meta-analysis.

13 DR. LEWIS: Thank you. Dr. Wang and then
14 Dr. Braunstein. And if you have a specific slide
15 you want to refer to, please let us know.

16 DR. WANG: Yes. I think I'll start just by
17 echoing Dr. Khosla's comment. I also feel -- I
18 think most people would acknowledge -- that an
19 observational study will not answer the scientific
20 question of whether romo is associated with
21 increased cardiovascular risk, given all the
22 problems that have been raised. But that doesn't

1 diminish the potential value of an observational
2 study for answering the question of the
3 cardiovascular risk experienced in the real world
4 by patients who might be taking this drug.

5 So that being said, if hypothetically one
6 were to consider a CVOT and one were to try to
7 target that in a population reasonably close to the
8 indicated population, so not unrealistically
9 enriched, have you considered the size of the study
10 that would be required to do that?

11 I'm looking at MACE rates of 1 to 2 percent
12 at 12 months. It seems impractically large, but
13 you must have considered some of those numbers.
14 What are the sample sizes we'd be talking about?

15 DR. KEHOE: We have not specifically looked
16 at what an outcomes trial would entail, how large
17 it would be, or anything like that, at this point

18 DR. JOFFE: This is Hylton Joffe. We do
19 have some experience in other chronic diseases like
20 diabetes, where they've done cardiovascular
21 outcomes trial. I know, for those trials, for
22 example -- it depends also on how much risk you're

1 trying to exclude. That impacts the size and
2 duration of the trials.

3 For example, here, we see a difference
4 pretty quickly within a 1-year period. So if you
5 were doing a trial, we wouldn't envision you'd
6 necessarily need to do a very long trial, but those
7 are some of the considerations also in terms of
8 what the event rate would be and those kinds of
9 assumptions.

10 DR. WANG: Of course, the diabetes trials
11 are in patients with diabetes who already have a
12 powerful risk factor. And even in that setting,
13 many of these trials are done with people with
14 existing cardiovascular disease.

15 DR. JOFFE: Right. It gets back to this
16 issue of enriching the population and how much you
17 can reasonably do that, based on how it would be
18 labeled for use in clinical practice?

19 DR. LEWIS: Thank you. Dr. Braunstein and
20 then Dr. Gerhard.

21 DR. BRAUNSTEIN: Braunstein. This is for
22 Dr. Jung. Have you had an opportunity to do a

1 network meta-analysis on alendronate versus placebo
2 with other trials, not these trials, but other
3 trials, to see if there is a protective effect of
4 alendronate over placebo as far as cardiovascular
5 events are concerned?

6 DR. JUNG: We only conducted analysis based
7 on these two trials, and we did not consider other
8 literatures that have covered alendronate versus
9 placebo. So our analysis is restricted to these
10 two women trials.

11 DR. LEWIS: Thank you. Dr. Gerhard and then
12 Dr. Dmochowski.

13 DR. GERHARD: Tobias Gerhard. First, kind
14 of a clarifying comment with Dr. Khosla's comment
15 about the difference of the real-world impact
16 versus the question of risk, and I think Dr. Wang's
17 comment went to the same point.

18 I think it's a really critically important
19 distinction that we cannot answer the question of,
20 if we have concerns about the observational design,
21 if there is a risk associated with the drug,
22 regardless in what population and whether it's a

1 low-risk or a high-risk population.

2 We can describe the incidence of risk in the
3 population that the drug is used, but to make an
4 inference, as the risk conferred by the treatment,
5 that cannot be answered. That's important to
6 really understand that limitation.

7 Again, as I pointed out earlier, I have very
8 strong concerns about the ability to answer this
9 specific question with an observational study,
10 given that this is a new drug where the warning is
11 in the label. There was an advisory committee, and
12 we're trying to examine the risk for exactly what
13 is warned about in the label and what we're meeting
14 about in an advisory committee. So it's literally
15 the textbook example of when observational studies
16 struggle or are virtually guaranteed to fail.

17 On the flip side, we have the cardiovascular
18 outcomes trial. There are big questions about
19 feasibility in the population.

20 So my question to FDA would be, have you
21 thought about a mix of both, a large simple trial
22 situation in this population? Because there is a

1 precedent of large simple trials, a limited
2 precedent, but there has been, because of the other
3 limitations -- Dr. Liu gave a very comprehensive
4 overview of all the issues and limitations with
5 particularly the observational designs, many of
6 which are gradual and can be partially addressed.

7 It wouldn't be perfect in a pragmatic way in
8 a large simple trial, but they could be addressed
9 within a meaningful boundary of uncertainty. But
10 the issue of baseline randomization, I think, is
11 the one that makes the difference of whether the
12 study is meaningful or just guaranteed to fail.

13 DR. LIU: Wei Liu from Division of
14 Epidemiology. Yes, I agree with your comments. In
15 this case, confounding by indication or channeling
16 bias is very concerning, given the proposed box
17 warning. So the baseline randomization certainly
18 is a way to overcome the limitation.

19 In fact, the FDA in a recent published
20 guidance includes pragmatic trial as a method that
21 could be used in the postmarketing setting to study
22 drug safety issues.

1 So back to my slide 3, it depends on the
2 panel's concern about how important is the safety
3 signal and the level of position of the evidence
4 required, and how to determine what type of design
5 was the most appropriate.

6 DR. LEWIS: Thank you. Dr. Dmochowski?

7 DR. DMOCHOWSKI: Roger Dmochowski, a
8 clarifying question to Dr. Jung. In your NMA
9 presentation, I think you said your presumption for
10 romo was on an intention-to-treat basis. If that
11 is correct, if I heard you correctly, did you
12 repeat the analysis on the per-protocol exposure of
13 the drug? And if so, was there any difference in
14 your outcomes?

15 DR. JUNG: So we tried to keep the
16 randomized feature of each study. That question
17 can be expanded to why not use alendronate and
18 placebo directly, and are they directly comparable?
19 I would say no because this actually breaks the
20 randomization rule.

21 To preserve the randomization rule, we use
22 the summary statistics from each study. When we

1 calculate the indirect effect, we reversed the
2 hazard ratio. In the denominator, there is
3 romosozumab as a denominator for both studies, but
4 that denominator for romosozumab doesn't
5 necessarily mean they're identical.

6 So that's why the randomization can be
7 preserved and calculated in drug effect.

8 DR. LEWIS: Thank you. Dr. Orza, and then
9 Dr. Lincoff.

10 DR. ORZA: On slide number 16, the FDA
11 presented exactly the trade-off I was hoping to see
12 about the risk difference at month 12, and it's
13 similar to the analysis that the sponsor also
14 presented on CR-10, but the numbers are a little
15 different, and I wonder what that's attributable
16 to.

17 The FDA says that for 3 fewer hip fractures
18 per 1,000 people, we would have 9 additional MACE
19 events, but the one for the sponsor says, for 14
20 fewer hip fractures, we would have 4 additional
21 MACE events. So I don't know what the difference
22 there is in the calculations, but the FDA's is

1 clearly much more troubling.

2 Could you speak to the differences in your
3 analyses?

4 DR. KEHOE: Can you tell me the sponsor
5 slide you're referring to?

6 DR. ORZA: CR-10.

7 DR. LEWIS: Right now, you're looking at the
8 sponsor numbers, so maybe let's let the sponsor
9 weigh in and then Dr. Kehoe.

10 DR. WASSERMAN: It's just that Dr. Kehoe's
11 analysis was at 1 year. This is at 3 years, to
12 capture the totality of the benefit-risk.

13 DR. LEWIS: Is that correct?

14 DR. KEHOE: Yes. That would be the
15 difference. We focused on the year that the
16 romosozumab exposure occurs rather than getting out
17 much longer, where there is no romosozumab
18 exposure.

19 DR. ORZA: Maybe later, we can see the
20 sponsor's numbers for 1 year.

21 DR. LEWIS: Does sponsor have their 1-year
22 number?

1 DR. WASSERMAN: Yes. Slide up.

2 DR. LEWIS: If you need a minute, we can
3 just -- yes.

4 DR. WASSERMAN: No, we have them. They're
5 basically the same as Dr. Kehoe articulated. I
6 think the challenge obviously is that, as we've
7 shown you before, the benefit from 1 year of
8 romosozumab in terms of fracture risk reduction
9 accumulates. We cut off at 3 years, but it keeps
10 on going, as you saw in the Kaplan-Meiers that went
11 out to 4 years.

12 DR. LEWIS: Thank you. Dr. Lincoff?

13 DR. LINCOFF: Yes. Amplifying on
14 Dr. Gerhard's point about, with an observational
15 study in the population who will be receiving the
16 drug, we'll be able to say what the event rates are
17 in those patients, but we won't be able to say
18 whether or not that's higher or the same if those
19 same patients had been treated with therapies other
20 than this drug.

21 So the question is, in an observational
22 format, does the FDA have any precedent or

1 preference for one in which it's a prospective
2 observational without randomization, but including
3 only those patients in both the control and the
4 drug groups that would have met the boxed warning?

5 To minimize the channeling bias, if that was
6 done, which seems to be the irreconcilable bias and
7 just using a broad population, if you could
8 eliminate that bias with a registry-type design
9 that actually included only certain patients, do
10 you believe that the other adjustments for bias and
11 for confounding could give you some indication of
12 whether or not these event rates are comparable
13 between the therapies?

14 DR. LIU: This is Wei Liu. In addition to
15 the concern that we just pointed at, which is the
16 level of regulatory needs and desired precision, of
17 course we need to look at the data sources to be
18 used for this observational study, and appropriate
19 study design and statistical analysis approach
20 needs to be used to address the limitations.

21 It depends on what the sponsor's going to
22 propose, so we are going to review their plans and

1 then be able to make assessment of whether that
2 really addresses the research question to the level
3 that is acceptable.

4 DR. LEWIS: Thank you. Dr. Burman, and then
5 Dr. Kushner. We are really running short on time.

6 Oh. I'm sorry; one more FDA comment?

7 DR. LEE: Jenny Lee from Division of
8 Epidemiology. Just to add to Dr. Liu's response,
9 prospective patient registries, prospective study,
10 primary data collection has its advantage but also
11 has its limitations.

12 For example, sometimes prospective patient
13 registries encounter difficulties of low
14 enrollment. There may be loss of follow-up or
15 missing data. But it does have an advantage, but
16 it doesn't guarantee it can overcome the limitation
17 associated with the retrospective study.

18 DR. LEWIS: Thank you. Dr. Burman, and then
19 Dr. Kushner?

20 DR. BURMAN: Thank you. Ken Burman. Just a
21 quick question for the FDA. It seems to me the
22 critical question we're discussing is observational

1 study versus cardiovascular outcomes trial, and
2 part of the observational study relates to the
3 black-box warning.

4 Does the FDA have any good quantitative
5 information on how often, in the real world, a
6 black-box warning is actually followed?

7 (Laughter.)

8 DR. MOENY: David Moeny, Division of
9 Epidemiology. We haven't done a lot of analysis in
10 this zone. We have a few cases where we've looked
11 at things with black-box warnings and, for
12 instance, duration of therapy to see whether or not
13 prescribers were adhering to duration of therapy
14 limits. We did find that there was quite good
15 adherence in those cases.

16 I think, as you decrease the severity -- and
17 this is just me speaking personally -- of the
18 warning and the placement in the label, it's going
19 to get less attention. So things sitting in a
20 black box are much more likely to be listened to.

21 DR. LEWIS: Thank you. We're actually out
22 of time, but I'm going to take one last question

1 from Dr. Kushner.

2 DR. KUSHNER: Just for clarification, in
3 order to do a large trial, simple trial, you'd have
4 to enrich the population, and that would include
5 patients with a black-box warning.

6 How would you do that? How would the FDA
7 actually allow that? You'd have to enrich the
8 study. How would you do that in a regulatory way,
9 and how would you select those patients to enrich
10 that population?

11 DR. JOFFE: Right. You have to ensure
12 there's still equipoise and that it's ethically
13 appropriate to do a trial. I think we still
14 haven't figured out what would go in a box, even,
15 if this would get approved. I've heard the
16 company's proposed a recent MI or stroke, but I
17 haven't heard excluding, for example, patients who
18 might be at increased risk for other reasons.

19 So I think it would also depend what we end
20 up putting in a box.

21 DR. LEWIS: Thank you. At this point, it's
22 time to break for lunch. I apologize to those who

1 may not have gotten their question in. We do have
2 time for discussion later, but we're running into a
3 lot of busy agenda and a lot to accomplish.

4 We're going to reconvene in this room at
5 12:50, so we really have a short lunch hour because
6 of concerns about travel. But at that point, we
7 will be beginning the open public hearing session.

8 Please take any personal belongings with you
9 that you need. Panel members, please remember no
10 discussion of the meeting topic during lunch
11 amongst yourselves or members of the audience.

12 Thank you.

13 (Whereupon, at 12:03 p.m., a lunch recess
14 was taken.)

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

(12:51 p.m.)

Open Public Hearing

DR. LEWIS: Good afternoon. Thank you, everyone, for coming back so that we can get going with the afternoon agenda. We are going to start with the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. We'd like to ensure such transparency at the open public hearing session of the advisory committee.

The FDA believes that it is important to understand the context of every individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship you may have with a sponsor, its product, and if known, its direct competitors. For example, this financial information could include payments of your travel by the sponsor, payment for your lodgings or other

1 expenses in connection with your attendance at the
2 meeting.

3 Likewise, the FDA encourages you, at the
4 beginning of your statement, to advise the
5 committee if you do not have any such financial
6 relationships. If you choose not to address this
7 issue, it won't preclude you from speaking.

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

13 That said, in many instances and for many
14 topics, there will be a variety of opinions. One
15 of our goals today is for this open public hearing
16 to be conducted in a fair and open way, where every
17 participant is listened to carefully and treated
18 with dignity, courtesy, and respect. Therefore,
19 please speak only when recognized by the
20 chairperson. Thank you for your cooperation.

21 I'd like to ask speaker number 1 to step up
22 to the podium and introduce yourself, and state

1 your name, please, as well as any organization you
2 may be representing for the record.

3 DR. THOMPSON: Good afternoon. I extend my
4 thanks to the committee for including patients,
5 patient advocacy organizations, caregivers,
6 physicians, and their perspectives in the hearing
7 today.

8 I'm Elizabeth Thompson. I'm the CEO of the
9 National Osteoporosis Foundation, and a caregiver
10 to a father and a husband with osteoporosis, and a
11 friend and colleague to many breast cancer
12 survivors who are now living with osteoporosis.
13 I'm here of my own financial volition. I will
14 disclose that the sponsor is one of many that
15 provides financial support in the form of
16 unrestricted educational grants for programs for
17 our organization.

18 You've heard our numbers, but I believe they
19 bear repeating. They are so large in some cases,
20 that it's actually hard to think about personalized
21 medicine or individualized treatment in their
22 context. Osteoporosis is responsible for just

1 under 2 million fractures in 2018.

2 The societal cost to care for those patients
3 will total \$52 billion in just 22 years, a time
4 where some of us, many of us in this room will be
5 in our phase 2. The number of fractures will
6 escalate 68 percent, and costs will rise to \$87
7 billion annually. That's from research from
8 Dr. Michael Wicki and Dr. Andrea Singer.

9 Why will that happen? America's aging.
10 We're keeping people alive longer. We have great
11 medicines and great procedures. We can transplant
12 hearts and livers. We're advancing cancer care at
13 an incredible speed with phenomenal impact. But
14 even while we extend lives, we, physicians,
15 advocates, patients, caregivers, and regulators
16 grapple with the facts. There are no perfect
17 medicines and there is no good disease. In fact,
18 there's just a constant evaluation of the trade-
19 offs.

20 Last June, my friend, Shelly, went on the
21 hike of a lifetime in the Blue Ridge Mountains with
22 her daughter. At the end of the first day, she

1 broke her femur and had to be airlifted out. She'd
2 never been counseled about her risk for
3 osteoporosis after her breast cancer treatment and
4 aromatase inhibitor.

5 My friend isn't alone. Research tells us
6 that most breast cancers occurring in women older
7 than 50 are often estrogen receptor or progesterone
8 receptor positive, and AIs are a good treatment
9 option. They're good at doing their job, at
10 killing cancer, but they're tough on bones.

11 A member of our scientific advisory board
12 familiar with romo tells me that women and men,
13 because prostate cancer patients also get AIs as
14 well, that romo could be a good treatment option
15 for them.

16 As the former president of Susan G. Komen
17 for the Cure, let me be clear, these patients who
18 are getting osteoporosis as a result of their
19 previous treatments are not old, uninformed people.
20 They will come as dynamic advocates armed with
21 facts, good and bad, ready to be full participants
22 in decision making about health, and they will

1 demand options.

2 In October, my husband fell and had an
3 excruciating back pain for 5 days. After that, we
4 finally got a DEXA scan, and we learned that he has
5 osteoporosis in his hip and he had two
6 microfractures in his back. He'll start infusion
7 therapy this week, but he's 70. We need options
8 after this, especially if he's going to keep up
9 with me for the life we have planned.

10 My dad's story is heartbreaking for all of
11 us. He's just about 90 years old and has a bit of
12 dementia. Just before Thanksgiving, he fell while
13 getting up to go to the bathroom at night. He's
14 one of the statistics. He'll never return home.
15 He went from home, to the hospital, to rehab, to
16 long-term care. This proud man is not going to
17 have the end of life that he envisioned or that we
18 want for him.

19 Every year in the United States, there are
20 just under 2 million people who fracture their
21 bones. I've shared the stories of three of them
22 today. I stand here today representing more than

1 50,000 people who are active in my organization.
2 They want me to share with you that their
3 independence is important to them. They want to
4 live as long as possible as well as possible.

5 As the chief advocate to so many people, I
6 ask the committee to carefully consider how
7 important it is to give physicians and patients
8 options, and to trust that physicians and patients
9 will be able to work through the personal issues of
10 balancing risk and benefit. Thank you.

11 DR. LEWIS: Thank you. Could speaker
12 number 2 please step up to the podium? Introduce
13 yourself, including stating your organization you
14 are representing for the record.

15 MS. BLACK: Yes. Hello. Thank you. I'm
16 Judy Black, and I extend my sincere thanks for this
17 committee to include patients and patient
18 advocates. I think it's so important. I'm an
19 osteoporosis patient and chairman of the board at
20 the National Osteoporosis Foundation. I'm here of
21 my own financial volition. I will disclose that
22 the sponsor has been a donor for our organization

1 as a whole, but only with financial support of
2 unrestricted educational grants.

3 I grew up as an athlete, a P.E. major in
4 Colorado, and honestly always expected to have a
5 high level of activity in my life. I also expected
6 that high level of athleticism that was in my
7 family would be good for me as a health protection.

8 All of that changed when I was diagnosed
9 with osteoporosis at the young age of 40 years old.
10 At that time, there weren't any medications on the
11 market, and I stopped doing a lot of the things
12 like skiing that I loved just because I was afraid
13 that they might be dangerous for me.

14 Over the last 25 years and through the
15 advances in science and the miracle of medicines,
16 I've moved from osteoporosis to osteopenia, and I'm
17 back to skiing. But I'm not out of the woods and I
18 know it. At some point, I'll need a new class of
19 medicine to protect my bones from crumbling,
20 cracking, so that I can get a really great squeeze,
21 a big hug, from one of my grandsons; so that I can
22 go on those bucket-list trips that I've envisioned

1 as I retire; and that I can fiercely and forcefully
2 advocate for the millions of osteoporosis patients
3 that can't be here with us today.

4 Isn't this what phase 2 of all of our lives
5 should look like, an active vigorous life? But
6 this is a disease that is way too often, way to
7 common. It impacts 1 in every 2 women over the age
8 of 50 and 1 in every 4 men over the age of 50, and
9 not just with a diagnosis of osteoporosis, but with
10 actual fractures.

11 Every year in the United States, just under
12 2 million people fracture their bones. They aren't
13 just nameless, faceless, old people. They are our
14 parents, our grandparents, maybe our favorite
15 teacher, perhaps our first boss. They are smart
16 people, talented people, people that have given so
17 much to this country and to the world. And yet,
18 because of a debilitating disease, they are not
19 here standing tall with me to advocate for other
20 options.

21 Out of the 2 million people who had
22 fractures this last year, there are 300,000 of them

1 who experienced hip fractures. To be direct,
2 75,000 of those people are not here talking with
3 you today. They're not even able to write letters
4 because, you see, they passed away because of
5 complications to their hip fractures.

6 Another 75,000 people healing from their hip
7 fractures can't be with us because they were forced
8 to leave their homes and have been stripped of
9 their independence, upending the rest of their
10 lives by being institutionalized and being taken
11 care of.

12 The remaining 150,000 can't be with us
13 today, or many of them, because the majority of
14 them never regained their previous function. Only
15 a small percentage of those folks can walk across a
16 room without a walker or a cane.

17 Death, the loss of independence, the loss of
18 dignity, that's not what any of us in this room
19 want. We already know what older people want. A
20 study from the National Conference of State
21 Legislators and the AARP, as well as other studies,
22 confirm time and again that the vast majority of us

1 just want to live our lives in our own homes and
2 our own communities as we age, and if possible, to
3 stay independent and adding to society. In fact,
4 isn't that what every single one of us in this room
5 want?

6 Part of living well and living independently
7 means healthy bones or at least healthier and
8 stronger bones. And that means physicians and
9 patients will need options, many options to treat
10 osteoporosis, if we do follow the new adage, treat
11 to 100.

12 Central to today's meeting regards
13 cardiovascular safety of the drug romo. I
14 challenge the committee to remember that at the
15 heart of this is shared decision making, that
16 prescribing this medicine, just as prescribing all
17 medicines, requires a discussion of the risks and
18 benefits between patients and physicians, and I
19 thank you so much for your time at this hearing.

20 DR. LEWIS: Thank you. Would speaker
21 number 3 please come forward, introduce yourself?
22 State your organization that you are representing

1 for the record.

2 DR. SRINIVASAN: Good afternoon. Thank you
3 for the opportunity to speak today. My name is
4 Dr. Varuna Srinivasan. I'm a physician with the
5 Masters of Public Health from Johns Hopkins
6 University and a senior fellow at the National
7 Center for Health Research.

8 We analyze scientific and medical data to
9 provide objective health information to patients,
10 health professionals, and policymakers. We do not
11 accept funding from drug and medical device
12 companies, so I have no conflicts of interest.

13 I would like to commend Amgen for conducting
14 several long-term studies with adequate racial
15 representation. Unfortunately, they had several
16 shortcomings that make it difficult to know who is
17 most likely to benefit from this drug and who is
18 most likely to be harmed.

19 Vertebral fractures are common in
20 postmenopausal women over the age of 65, and many
21 of them are asymptomatic, and many never cause pain
22 or health problems. The study results indicate

1 that the drug reduces the risk of vertebral
2 fractures for postmenopausal women with
3 osteoporosis, but the absolute risk goes down only
4 1 percent during the first year and less than
5 2 percent the second year.

6 That is a very small tiny risk and does not
7 benefit 98 percent of patients. In the
8 manufacturer's efficacy studies, the fractures are
9 evaluated only via morphometric and radiological
10 assessments. As such, they do not measure
11 meaningful outcomes for the patients such as pain
12 and other quality-of-life indicators.

13 What are the clinical implications of these
14 fractures based on radiographic evidence rather
15 than clinical symptoms? More importantly, while
16 the reduction in vertebral fractures in some of the
17 measures was statistically significant, the
18 absolute risk remains small, and the safety results
19 indicate an increase in immediate adverse
20 cardiovascular disorders.

21 So the question for this advisory committee
22 should be, which patients are more likely to

1 benefit than be seriously harmed, or die as a
2 result of these drug? The sponsor has not
3 conducted those types of analyses, and they are
4 needed before considering approving this drug.

5 The meta-analysis showed an increase of
6 MACE. We do not know yet if that is an increase on
7 average for all patients or if some patients are at
8 an even higher risk while others are not.

9 Additional clinical trials are necessary to
10 determine whether some types of patients are more
11 likely to benefit without an increased risk of
12 severe cardiovascular event.

13 Such research should examine potentially
14 influential characteristics such as age, previous
15 history of cardiovascular disease, and drug
16 interactions. This is important information that
17 should be evaluated before the drug goes on the
18 market for 2 reasons. Patients cannot make
19 informed decisions without it. Trying to obtain
20 this information from post-approval, real-world
21 evidence would be very difficult.

22 Once a drug is on the market and advertised,

1 far more people are exposed to its potential side
2 effects and interactions than would be the case in
3 a premarket clinical trial. Relying on postmarket
4 databases and registries to tell us which groups of
5 people are at risk is a reasonable strategy for
6 some treatments, but does not make sense in the
7 situation because the benefits are relatively
8 modest compared to the life-threatening
9 cardiovascular risks.

10 To protect patients from serious harm, the
11 sponsor needs to re-analyze the data or collect new
12 randomized double-blind study data to enable them
13 to identify the patients for whom the benefits are
14 the most likely to outweigh the risks.

15 In the interests of patient safety, we
16 respectfully urge the committee today to require
17 the manufacturer to reanalyze the data they have to
18 focus on which patients are most likely to show
19 meaningful benefit, meaning reduced hip fractures,
20 and which are most likely to have cardiovascular
21 harm.

22 If such analysis is inconclusive, the

1 sponsor should be required to conduct additional
2 premarket safety outcome trials for this drug
3 before approval to determine which patient groups
4 would best benefit from this drug and which should
5 avoid it. Thank you.

6 DR. LEWIS: Thank you. Could speaker
7 number 4 please come to the podium? State your
8 name and the organization that you represent.

9 DR. ALADDIN: Good afternoon. My name is
10 Dr. Aladdin, and I'm a health researcher at Public
11 Citizen Health Research Group. I have no financial
12 conflicts of interest.

13 This is a second cycle of review for
14 romosozumab, and on July 13, 2017, the FDA issued a
15 complete response letter after the applicant
16 completed two additional trials comparing romo to
17 placebo and the active comparator, alendronate.

18 Trial 142, for short, was an alendronate-
19 controlled fracture trial in postmenopausal women
20 with osteoporosis and trial 174 was a placebo-
21 controlled bone mineral density study in men with
22 osteoporosis.

1 Now, these trials certainly demonstrated
2 efficacy but raised concerns, as there was an
3 increased risk in cardiovascular serious adverse
4 events in the year of romo treatment in both
5 studies. We strongly urge the committee recommend
6 that the FDA not approve romo.

7 Just an overview of the mechanisms of
8 action; sclerostin is a product of the SOST gene,
9 and it is endogenous antagonist of a signaling
10 pathway cascade. Loss of function can lead to
11 excessive bone formation. While sclerostin is
12 primarily expressed by osteoclast, it's also
13 expressed by a number of other tissues, including
14 the heart and the aorta, while its function still
15 remains unknown.

16 Romosozumab is a monoclonal antibody that,
17 as you can see, inhibits sclerostin and at least an
18 increase in activation of this one signaling
19 pathway. There are important safety concerns
20 because when signaling is actually involved in many
21 different physiological and cellular roles, it's
22 important to consider the potential for offshoot

1 effects of targeting a signaling pathway that plays
2 such diverse roles in maintaining other vital
3 cellular functions.

4 Furthermore, this pathway also plays a role
5 in vascular endothelial cells. There's a growing
6 body of evidence to suggest that when signaling is
7 also involved in cardiovascular disease, it's
8 actually also being targeted as a potential
9 therapeutic.

10 This table was presented earlier at this
11 meeting, and what we see here in the alendronate
12 and romo trials is an increase in hazard ratio with
13 a low of 1.42 and high of 3.21, an increase in
14 cardiovascular adverse events. We didn't see these
15 increased hazard ratios in the placebo trial, and
16 this remains unknown and unclear.

17 There is also a lack of evidence
18 demonstrating the cardioprotection by alendronate.
19 The placebo-controlled fracture trial did not show
20 a cardiovascular safety signal. However,
21 alendronate controlled fracture trial 142 and the
22 smaller BMD trial 174, in men with osteoporosis,

1 did show a cardiovascular safety signal.

2 Furthermore, there's no definitive evidence
3 to suggest that alendronate is cardioprotective, so
4 after conducting additional exploratory analyses,
5 neither the applicant nor the FDA have been able to
6 conclusively determine the cause for the discrepant
7 MACE results between the placebo-controlled
8 postmenopausal osteoporosis trial and the other two
9 phase 3 trials.

10 In another point made by the FDA, the
11 multivariate network meta-analysis results adjusted
12 by treatment group and age and stratified by
13 country did not differ from the univariate
14 analysis. This finding suggests that the rate of
15 MACE with alendronate was lower than that of
16 placebo, but is limited by cross-study comparisons
17 and cannot definitively establish whether
18 alendronate is cardioprotective. Furthermore, we
19 also saw in the placebo trial in men, that there
20 was an enhanced safety signal for cardiovascular
21 risk.

22 In conclusion, while this drug is effective

1 in increasing bone mineral density and decreasing
2 vertebral fractures in both placebo- and
3 alendronate-controlled clinical trials, its effects
4 some cardiovascular adverse outcomes in alendronate
5 clinical trials and raises safety concerns that
6 must be resolved prior to approval.

7 The effects of alendronate on the
8 cardiovascular system have not been fully
9 understood, and there is no evidence that this drug
10 is cardioprotective. Furthermore, targeting a
11 pathway as versatile as the one signaling pathway
12 has the potential to confer additional unforeseen
13 risks.

14 Consistent with the precautionary principle
15 of public health, we strongly urge the committee to
16 recommend that the FDA not approve romo. Thank
17 you.

18 DR. LEWIS: Thank you. Could speaker
19 number 5 please approach the podium? Don't forget
20 to state the name and organization that you
21 represent for the record.

22 DR. SINGER: Good afternoon. I'm Dr. Andrea

1 Singer, an in-the-trenches practicing primary care
2 provider, as well as a bone health specialist who
3 directs the fracture liaison service or secondary
4 fracture prevention program at MedStar Georgetown
5 University Hospital here in D.C.

6 I'm also chief medical officer at the
7 National Osteoporosis Foundation, a position for
8 which I have volunteered for the past number of
9 years because I am passionate about improving the
10 care and lives of patients with osteoporosis and
11 fractures. I'm here to offer a clinician's
12 perspective on osteoporosis care and also put a
13 face to this disease. I'm here of my own financial
14 volition.

15 There are many patients that we see in
16 practice who make lasting impressions on us. I
17 want to tell you about one whose story stays with
18 me and illustrates how devastating osteoporosis can
19 be, especially in ways in which we might not
20 normally consider.

21 My patient was a women in her 70s who had
22 several vertebral fractures by the time she came to

1 see me. Despite treatment with various
2 osteoporosis medications, she continued to
3 fracture. She had chronic pain, and it became more
4 difficult for her to get around. She always came
5 into the office to see me either early in the
6 morning or at the very end of the day. And for
7 those of you who live in this area or who tried to
8 get here this morning, you know that those are
9 absolutely the worst times to try to navigate D.C.
10 traffic.

11 As she was retired, I asked her why she
12 didn't make an appointment during the middle part
13 of the day when it would be easier to get in,
14 figuring that somehow it was related to her pain or
15 mobility issues.

16 Her response was, that as a result of her
17 spine fractures, she hated her appearance, felt she
18 could not find clothes that fit properly, and could
19 only consider coming at a time when she would be
20 seen by the fewest number of people. She could not
21 face a waiting room full of patients looking at
22 her, and indeed, gradually avoided going out in

1 public, socializing, or going to family gatherings
2 unless she absolutely had to.

3 While this may seem like an extreme case,
4 she is the type of patient I see all of the time in
5 practice, someone who has had one or more
6 fractures, someone for whom a fracture has been a
7 life-altering or life-threatening event, and
8 someone for whom having additional treatment
9 options might change or impact the course of her
10 disease.

11 Why do we need additional treatment options?
12 Ideally, to help us prevent fractures, to do so
13 quickly, and to do so in a sustained fashion,
14 something we are not adequately doing at this time
15 in clinical practice.

16 Though there are not many osteoporosis
17 emergencies, osteoporosis doesn't develop
18 overnight, if ever there were to be an osteoporosis
19 emergency or urgency, it's in a patient who has had
20 a first fracture, as the risk for a current
21 fracture is greatest in the 1 to 2 years following
22 that prevalent fracture.

1 Having a new treatment options such as
2 romosozumab, one that rapidly increases bone
3 density and bone strength and reduces the risk for
4 fracture, would be an important tool in our
5 treatment armamentarium.

6 In addition to the acute treatment issues,
7 osteoporosis is a chronic disease, and as with
8 other chronic diseases such as diabetes and
9 hypertension, things that I treat every day as
10 well, it requires long-term management, including
11 lifestyle and behavioral changes, as well as
12 pharmacologic therapy.

13 In contrast to many of the medications used
14 in these other chronic diseases, our current
15 bone-forming agents have a lifetime duration of use
16 limitation even though disease and risk continue
17 without limitation.

18 The more options we have in the
19 armamentarium, the more likely it is that we can
20 find an appropriate treatment or treatment sequence
21 for each individual based on her clinical risk
22 factors, her goals of treatment, her individual

1 risk profile, and her individual preferences, and
2 ultimately make a difference in the course of
3 disease for the millions of women with osteoporosis
4 at high risk for fracture.

5 All medications have risks, and I clearly
6 understand the concerns regarding potential
7 cardiovascular issues with romosozumab, but
8 efficacy and choice do remain important. It is our
9 role and, indeed, incumbent upon us as clinicians
10 to practice effective risk communication and engage
11 in a shared decision-making process with our
12 patients to help them understand the risks
13 associated with the disease itself with
14 osteoporosis and fractures and also understand the
15 options for treatment, including the risks,
16 benefits, alternatives, and uncertainties. Thank
17 you for your attention.

18 DR. LEWIS: Thank you. Could speaker
19 number 6 please come to the podium? Introduce
20 yourself and state the name of your organization
21 for the record.

22 MR. WYLAM: Hello. My name is John Wylam,

1 and I'm the staff attorney for Aimed Alliance.
2 Aimed Alliance is a 501(c)(3) nonprofit
3 organization that seeks to protect and enhance the
4 rights of healthcare consumers and providers. I
5 have no conflicts of interest to disclose. A list
6 of Aimed Alliance collaborators can be found on our
7 website.

8 Thank you for the opportunity to comment on
9 the pending application of a new bone-building
10 agent for the treatment of postmenopausal women at
11 high risk of fracture. I request that the FDA
12 approve this new bone-building agent because it
13 will fill unmet needs for these patients.

14 For osteoporosis patients, approving this
15 medication may improve medication adherence and
16 foster greater health outcomes. Additionally,
17 approving this medication will create more
18 competition in the market, which should reduce
19 prices for consumers.

20 Osteoporosis is a disease resulting from low
21 bone mass and structural deterioration of bone,
22 which increases the risk of fractures of the wrist,

1 hip, and spine. Osteoporosis can cause bones to
2 become so brittle that a fall or mild stresses such
3 as bending over or coughing can result in a
4 fracture. These fractures can result in pain,
5 disability, placement in a nursing home, increased
6 healthcare costs, and death.

7 Osteoporosis affects 10.2 million older
8 adults in the U.S., including one quarter of all
9 American women aged 65 or older. Approximately
10 50 percent of women over the age of 50 will
11 experience a hip, wrist, or vertebral fracture in
12 their lifetime. To prevent bone deterioration and
13 fractures and to improve overall quality of life,
14 individuals with osteoporosis must have access to
15 affordable and effective treatment options.

16 Medications that treat osteoporosis aim to
17 reduce the risk of fractures. These medications
18 include antiresorptive and anabolic treatments.
19 Antiresorptive medications tend to slow bone
20 resorption rates while anabolic medications tend to
21 increase bone formation. The common approach to
22 osteoporosis treatment includes using a

1 bisphosphonate antiresorptive medication that slows
2 bone resorption. This is done to slow the process
3 of bone resorption in an attempt to improve bone
4 mineral density and reduce the frequency of
5 fractures.

6 While this approach works for many patients,
7 antiresorptive medications may not fully address
8 the needs of some postmenopausal women at a high
9 risk of fracture who have already lost a
10 significant amount of bone mineral density.

11 In these patients, antiresorptive
12 medications are not able to improve bone mineral
13 density enough to effectively mitigate fracture
14 risk. Current research suggests that a combination
15 approach of stimulating bone formation with an
16 anabolic medication before inhibiting bone
17 resorption with an antiresorptive medication could
18 offer a promising solution for these patients.

19 The bone-building agent under FDA
20 consideration is an anabolic treatment that enables
21 such a combination approach. While existing
22 anabolic therapies are only able to stimulate bone

1 formation in combination with bone resorption, this
2 innovative anabolic therapy under FDA consideration
3 stimulates bone formation without also stimulating
4 resorption.

5 Preliminary studies indicate that this may
6 result in a significant increase in bone mineral
7 density. By stimulating bone tissue formation
8 before the patient is placed on antiresorptive
9 medication, the patients bones may be reinforced
10 before the antiresorptive medication is used to
11 prevent the new tissue from being resorbed.

12 If approved, this medication could bring
13 relief to osteoporosis patients who previously may
14 not have had effective treatment options due to the
15 progression of their condition. Treatment
16 adherence can be challenging for osteoporosis
17 patients. Osteoporosis medications must be taken
18 for up to a year to be effective, but many patients
19 discontinue their medication without completing the
20 full course of treatment.

21 According to a survey by the International
22 Osteoporosis Foundation, as mentioned earlier, up

1 to 60 percent of patients who took a once-weekly
2 anti-osteoporotic medication and nearly 80 percent
3 of patients who took a once-daily anti-osteoporotic
4 discontinued treatment within a year. This
5 indicates that the frequency of medication
6 administration can have a negative effect on
7 medication adherence.

8 New bone-building agents could help
9 alleviate this issue. The only comparator
10 medications currently available require daily
11 subcutaneous injections, whereas the new bone-
12 building agent may be administered once per month.

13 Additionally, healthcare providers would
14 administer the medication directly, which would
15 likely improve patient monitoring and adherence to
16 the treatment plan. Increased adherence would
17 likely support improved health outcomes.

18 Only two anabolic medications for the
19 treatment of osteoporosis are available in the
20 United States, and they can be quite expensive.
21 The approval of a third option would introduce new
22 competition into the market and may put downward

1 pressure on the prices of currently available
2 medications. Providing osteoporosis patients with
3 more affordable treatment options will undoubtedly
4 improve their medication adherence along with their
5 health outcomes.

6 For these reasons, I again ask the FDA to
7 approve this medication for the treatment of
8 postmenopausal women at high risk of fracture.
9 Thank you for your time.

10 DR. LEWIS: Thank you. Could speaker
11 number 7 please approach the podium, and state your
12 name as well as the organization that you
13 represent? Thanks.

14 MS. CODY: Thank you for your time today.
15 My name is Kathleen Cody, and I'm the executive
16 director of American Bone Health. We're a national
17 community-based, nonprofit organization, and to be
18 completely transparent, our organization receives
19 contributions and educational grants from
20 individuals, from foundations, and from
21 corporations, including Amgen. I'm here today at
22 my own expense.

1 American Bone Health does public education
2 about osteoporosis and fracture prevention through
3 a national network of trained pure educators. Last
4 year, our peer educators reached over 1 million
5 older adults with tools and information about bone
6 health.

7 Today, I'm here to represent them and the
8 other 52 million Americans who are at risk for
9 fractures because of poor bone health. I support
10 the addition of a new therapeutic option for them
11 because we continue to have a national public
12 health crisis when it comes to osteoporosis and
13 fractures.

14 Poor bone health is a problem for millions
15 of older adults. Poor bone health mostly affects
16 women. Women have 3 times as many osteoporotic
17 fractures as men. Poor bone health affects the
18 independence and the quality of life of those
19 patients and the people who care for them.

20 There are 2 million preventable fractures
21 each year, and the worst of those fractures is the
22 hip fracture. Hip fractures represent about

1 one-quarter of those preventable fractures or about
2 300,000 a year. Of those, as you've already heard,
3 about 24 percent of those patients will die within
4 a year, but not before a considerable amount of
5 healthcare dollars are spent on them.

6 Everyone I speak to knows of someone who's
7 fallen, broken their hip, gone to the hospital, and
8 never come home. You'll rarely find the cause of
9 death as a hip fracture. The cause of death will
10 be listed as pneumonia, or pulmonary embolism, or
11 sepsis, not the hip fracture that landed them in
12 the hospital in the first place.

13 The reason these hip fracture numbers are
14 significant is because they're increasing. After a
15 steady decline since 2002, hip fractures appear to
16 be on the rise. Between 2013 and 2015, there were
17 11,000 more hip fractures than we expected at a
18 cost of about \$460 million. This alarming trend is
19 due in part to declines in screening, declines in
20 treatment, and an increase in chronic conditions
21 like diabetes.

22 The reason that the increases in hip

1 fractures is so tragic is because we know how to
2 effectively screen, and diagnose, and treat
3 osteoporosis, and yet osteoporosis remains
4 underdiagnosed and undertreated.

5 The current first-line treatment for
6 osteoporosis was approved in 1996. With the
7 advances in research, diagnosis, and personalized
8 medicine, there is a need to better individualize
9 osteoporosis treatment. My mother has been on this
10 first-line treatment for osteoporosis since 2014,
11 but she is still having spine fractures, as
12 recently as November.

13 Her pain is debilitating. She's often
14 forced to bed despite the need to take care of my
15 father. For a long time, she avoided pain
16 medicines because they made her loopy. But now,
17 she regularly resorts to a cocktail of painkillers
18 just so she can function.

19 My mother would benefit from a change in her
20 therapy. She has diabetes and digestive tract
21 problems, and in retrospect, is probably not
22 absorbing her current medicine. If there is one

1 thing that I can do, it's to advocate for new
2 scientific discoveries that create and bring to
3 market new medicines that can better benefit
4 individual patients like my mother.

5 Although osteoporosis and fractures are a
6 public health crisis, they're a personal crisis for
7 millions of Americans and their families. With the
8 aging population, we must welcome innovative
9 solutions that could close the gap from our best
10 evidence-based practices and the dismal outcomes
11 that we are seeing in osteoporosis care.

12 With every new therapy, we can get closer to
13 an eventual cure for osteoporosis, maybe not in
14 time for my mom, but maybe in time for other moms.
15 Thank you.

16 DR. LEWIS: Thank you. Could speaker
17 number 8 please come to the podium? Introduce
18 yourself and state the organization that you are
19 representing for the record.

20 MS. MARPLE: Good morning. My name is Judy
21 Marple. I'm here on behalf of the Global Healthy
22 Living Foundation, which paid for my travel here

1 today. The foundation accepts grants and
2 charitable contributions from pharmaceutical
3 companies, government, private foundations, and
4 individuals. Its medical team has been briefed on
5 osteoporosis by independent scientists and
6 physicians, as well as representatives from
7 pharmaceutical companies.

8 I would like to thank the FDA for this
9 opportunity to provide comments today. I have
10 osteoporosis. I am here representing other
11 patients like me with osteoporosis as well, as the
12 Global Healthy Living Foundation, a 501(c)(3)
13 patient organization representing chronically ill
14 patients and their caregivers across the U.S.,
15 Western Europe, Australia, and South America. GHLF
16 works to improve the quality of life for people
17 living with chronic disease by making sure their
18 voices are heard and advocating for access to best
19 practice medical care.

20 I'd like to start by speaking about my own
21 personal journey with osteoporosis. This disease,
22 coupled with the inability to find an effective and

1 lasting treatment, has caused a substantial burden
2 on my everyday life. This journey started 3 years
3 ago, when I had my first fracture. Two to 3 months
4 later, I had a second fracture. Concerned, I
5 immediately went to a specialist who started me on
6 physical therapy or PT. Additionally, I began
7 trying various osteoporosis drugs.

8 As you can imagine, going through physical
9 therapy with a broken body was painful, but I
10 wanted to walk, sit, and stand normally again. At
11 the same time, I was feeling ill from the side
12 effects of the drugs being prescribed to help me
13 get better. I endured these difficulties by
14 staying motivated by the thought of getting back to
15 the job I love, and most importantly, getting back
16 behind the wheel to see my grandchildren. After a
17 year of rehab with my doctor's help, I was able to
18 accomplish these goals.

19 Unfortunately, this year has taken a turn
20 for the worse, and despite my best attempts at
21 being as careful as possible, I've had 4 new
22 fractures. That's a running total of 6 bone

1 fractures, 5 vertebral fractures and one sacral
2 insufficiency fracture.

3 These fractures have caused changes in the
4 shape of my body. I have kyphosis and daily pain.
5 I'm unable to stand, walk, or sit without
6 discomfort. Much to my disappointment, I had to be
7 placed once again on disability and am no longer
8 able to work. What is even more disappointing is
9 that I have exhausted all options currently
10 available to treat osteoporosis and risk status for
11 my fractures remains high. I am deeply concerned
12 about my quality of life moving forward if new
13 therapeutic options do not become available.

14 My story is unfortunately a common one.
15 Many people like me exist, people who have been
16 waiting for another option for years. However, I
17 am hopeful for myself and many others who could
18 benefit from the new drug being considered today.
19 The fact that there may be a new option and that
20 people taking romo have shown impressive gains in
21 bone density is very exciting. The first-in-class
22 medication will be a welcome addition to the drugs

1 we already have and feel some important needs.

2 I am here today to put a face to the
3 thousands of patients who will immediately benefit
4 from treatment of bone-building and bone
5 degradation prevention drugs such as this one. We
6 are optimistic about our future, considering that
7 romo could potentially change our lives and give us
8 our independence back.

9 I am optimistic about my future. I am 60
10 years young and have a full life to live. I long
11 for the day that I am able to get back to work, to
12 go to the store without having to stretch, push
13 myself, and I can't wait to get in that car and go
14 and visit my own grandchildren as many times as I'd
15 like.

16 Thank you for considering my story and
17 comments as you deliberate today. I will be
18 submitting written comments on behalf of GHLF to
19 the formal docket. If you have any additional
20 questions, I'm available today to answer them. And
21 I do want to say thank you very much. I appreciate
22 your letting me speak.

1 DR. LEWIS: Of course, thank you.
2 Speaker 9, please come to the podium, introduce
3 yourself, and tell us the organization that you
4 represent so that it can be entered into the
5 record.

6 MR. SCHALL: Thank you. My name is John
7 Schall. I'm the chief executive officer of
8 Caregiver Action Network. Caregiver Action Network
9 is the National Family Caregiver's Association. We
10 are the nation's leading consumer-facing nonprofit
11 association, providing information and resources
12 to the 90 million Americans across the country who
13 are caring for their loved ones with chronic
14 conditions or other situations.

15 Thank you for the opportunity to speak in
16 support of new options for osteoporosis. There are
17 no financial supports for my appearance here today,
18 but I will say that the sponsor is one of more than
19 40 companies that make donations to the Caregiver
20 Action Network for its nonprofit educational
21 programs across the country.

22 It is critical that patients and family

1 caregivers have additional treatment options for
2 preventing and then treating osteoporosis. I would
3 like to remind you that there's an important family
4 caregiving component to both the prevention side
5 for osteoporosis and certainly for caring for those
6 loved ones, especially after a fracture.

7 There are currently only 2 bone-building
8 agents available on the market and more are needed.
9 The existing therapies don't work for all patients.
10 And I will tell you that my mother is one of those
11 for whom existing treatments are not effective.
12 She is a breast cancer survivor, and I assure you
13 that we live in worry every day of the next
14 possible fracture with my mother.

15 But it isn't just my mother. With
16 10 million people with osteoporosis, there are
17 10 million families that are affected as well.
18 Even though at Caregiver Action Network, we help
19 families with their loved ones, really, of every
20 chronic condition, when you think of the numbers of
21 people affected by fractures from osteoporosis, you
22 can see why we hear from these family members all

1 the time.

2 For women, the incidence is greater than
3 heart attack, stroke, and breast cancer combined,
4 and for men, it's more frequent than incidents of
5 prostate cancer. So for our community, this is a
6 hugely important issue.

7 I would like to say that when a fracture
8 occurs, the family caregiving role is then even
9 more important and even more challenging. The very
10 useful statistics that come from the National
11 Osteoporosis Foundation are important, but I must
12 tell you they're also quite frightening to us as
13 families across the country; that every year, of
14 nearly 300 hip fracture patients, one quarter of
15 them end up in nursing homes and half never regain
16 their previous function.

17 At 6 months after a hip fracture, only
18 15 percent of patients, our family members, can
19 walk across a room unaided. And as you've heard
20 from others saying today, a quarter of those hip
21 fracture patients over the age of 50 will die in
22 the following year. And for older patients,

1 obviously, that mortality and morbidity rate is
2 even higher, one that I constantly think of with
3 respect to my mother.

4 I think one of the most frightening
5 statistics for us is that even after a fracture, 4
6 out of 5 patients are not treated, even diagnosed,
7 or necessarily tested for osteoporosis. We can
8 certainly do better. We need more treatment
9 options.

10 I would be negligent if I didn't speak
11 directly to the question of risks and benefits. I
12 want to say that patients and families are
13 extremely, acutely, intensively aware that any
14 treatment option will have risks and benefits.
15 Certainly, in the last few years, as we've moved to
16 more focused patient-centered care, patients and
17 families understand this even more.

18 Shared decision-making is not simply a
19 phrase that we use. My organization actually goes
20 across the country, training patients and family
21 caregivers on the shared decision-making process
22 with their healthcare professionals.

1 It is very clear that what patients and
2 families want are additional options available to
3 them and information about risks and benefits that
4 they can discuss with their healthcare providers to
5 find the best treatment plan for them.

6 Patients and families are not afraid of the
7 risk and benefit conversation. They know it,
8 they're getting familiar with it, and they can
9 handle it with their doctors. So we definitely
10 need more treatment options here in the
11 osteoporosis space. Thank you for the opportunity
12 to speak with you today

13 **Clarifying Questions to Applicant or FDA**

14 DR. LEWIS: Thank you.

15 Thank you to all of our speakers. This
16 concludes the open hearing public portion of the
17 meeting. We'll no longer take comments from the
18 audience. The committee will now turn its
19 attention to address the task at hand, the careful
20 consideration of the data before the committee as
21 well as the public comments.

22 Before we get to the formal discussion

1 questions, however, we do have opportunity to talk
2 about any additional clarifying questions for
3 either the sponsor or the FDA, so we'll go through
4 the usual process.

5 Please remember, if you have a question to
6 state your name for the record before you speak and
7 identify which presenter the question is for or if
8 it's general for all presenters.

9 We'll start with Dr. Lincoff.

10 DR. LINCOFF: Yes. I have a question for
11 the sponsor. Could you clarify or maybe provide
12 more information about why you've made a decision
13 that the treatment duration should be for 1 year?
14 I recognize in the curves that you showed, that the
15 density appears to level a bit, but it's still
16 increased.

17 Do you anticipate this will be used for
18 multiple courses of 1 year over the course of a
19 lifetime? Many of the speakers have talked about
20 the issue of existing therapies are only indicated
21 for up to 2 years for a patient's life, so maybe
22 some more information would be helpful.

1 DR. WASSERMAN: Sure. Thanks, Dr. Lincoff.
2 The rationale behind the 12 months was to basically
3 build a foundation of bone, after which we would
4 then transition to an antiresorptive. And it was
5 based primarily on two concepts. One is when we
6 look at the increase in BMD over time, it begins to
7 level off. I think you can see -- slide up -- this
8 is from the benefit-risk discussion that we had a
9 little bit earlier, but the curve in blue is
10 representative of what you would see.

11 This is from study 337. You can see that
12 most of the BMD gains are in the first 6 months,
13 and then the slope begins to decrease, but it's
14 still basically going up from 6 months to a year.
15 It begins to level off thereafter. And what we
16 found by looking at bone turnover markers,
17 et cetera, was that the rate of bone density
18 increases after 1 year was very similar to what you
19 could get with an antiresorptive.

20 So we made a decision to basically
21 transition to an antiresorptive at that time, but
22 there's no reason to prevent someone from reusing

1 this therapy at a later time.

2 DR. LEWIS: Thank you. Dr. Khosla and then
3 Dr. Orza.

4 DR. KHOSLA: I had a question, actually, on
5 one of Dr. Karp's slides. It's slide 29 from her
6 presentation. The question is on the right panel.
7 Certainly, one interpretation of those findings is
8 what we've been discussing, the increase in CV
9 events with romo. Alternate interpretations we've
10 discussed is that, based on the first study, the
11 337 study, that there's no difference between the
12 placebo and the romo group, but that the true event
13 is actually closer to the romo group, and in fact,
14 there's a protective effect of alendronate.

15 So that point's already been made. The
16 question I'm raising is, it looks like that
17 protective effect, if there is one, is really in
18 the first 12 to 18 months, and then it seems to
19 disappear.

20 It raises the question of, when you compare
21 the CV events from the alendronate trials, if those
22 analyses are done at 36 at 3 or 5 years, you're

1 going to miss that early protective effect of
2 alendronate, which is potentially confounding the
3 interpretation of this data. I'm just curious on
4 your thoughts or of the Amgen group on that
5 possibility.

6 DR. KARP: I think one explanation is that
7 if alendronate has an early protective effect, it
8 may wane after a year. We also talked a lot about
9 the nonlinear incidence with alendronate overall in
10 study 142, which we don't have an explanation for.

11 DR. KHOSLA: So yes. I guess if the effect
12 wanes after a year, you wouldn't see it in all of
13 the analyses that have been presented that looked
14 at 3 to 5 years, because by then, that early
15 protective effect is basically gone.

16 DR. KARP: Right. So that's a possibility.

17 DR. WASSERMAN: Dr. Khosla, we have some
18 thoughts on that as well. I'd like to call
19 Dr. Marc Sabatine to the mic.

20 DR. SABATINE: Yes. It's an intriguing
21 observation for the notion of the shape of the
22 curve. and I guess it gets back to the two

1 possibilities. One is that there could be a very
2 protective effect of alendronate in that first
3 year, and the FDA's network meta-analysis then
4 speaks to that.

5 I would offer a little bit of caution.
6 Obviously, the analysis was technically correct.
7 They noted the limitations given the trials there.
8 That hazard ratio of 0.55, just to try to put that
9 in cardiovascular perspective, that's the benefit
10 of aspirin analytic versus no therapy for someone
11 coming into the ED with a STEMI. Right? I mean,
12 that's a ginormous benefit.

13 So I would be a little cautious about just
14 relying on those data. I think, again, the more
15 likely scenario for that stable population is it
16 should be a linear event rate.

17 I think, if any of us wearing an epi hat
18 were to have a cohort of stable individuals and
19 have roughly 100 events accrued over 3 to 4 years,
20 we would look at the entire time and figure out the
21 incidence rate, and probably not be tethered to
22 just a 12-month rate with basically less than 2

1 dozen events. So that's my take on the data.

2 DR. WASSERMAN: Dr. Lewis, I have the answer
3 to Dr. Khosla's question that he asked a little bit
4 early if you don't mind.

5 DR. LEWIS: Quickly.

6 DR. WASSERMAN: Sure. So we looked at the
7 UK Biobank, Dr. Khosla, and it had about
8 12,000 cases of myocardial infarction, nearly
9 6,000 cases of stroke. The p was greater than 0.10
10 for both, so no detectible effect.

11 I also looked at our Icelandic database
12 during the break. Looking at whether or not you
13 developed coronary artery disease before the age of
14 65, the odds ratio -- and then there was two
15 different SNPs in the Icelandic population -- was
16 1.02 with a 95 percent confidence interval of 0.99
17 to 1.05. The other SNP was 0.99 with a 95 percent
18 confidence interval of 0.91 to 1.07.

19 DR. ROSEN: Which SNPs were those?

20 (Laughter.)

21 DR. ROSEN: Because there's data that other
22 SNPs show a positive effect on bone and a negative

1 effect on cardiovascular.

2 DR. WASSERMAN: Dr. Rosen, I'll have to get
3 my computer.

4 DR. LEWIS: Thank you. Dr. Orza?

5 DR. ORZA: I have a few questions that flow
6 from public comments, and I can ask one and get
7 back online if that's what you'd prefer. There was
8 a lot of commentary about people actually having
9 osteoporosis therapy that is not working for them
10 or improving their situation.

11 I notice that in both 337 and 142, the
12 requirement for enrollment was no recent treatment
13 for osteoporosis. But do you have any data -- does
14 the sponsor have any data on people who were not
15 having success with a previous osteoporosis therapy
16 and what happened to them when they took the romo?

17 DR. WASSERMAN: Sure. So thank you for that
18 question. I'll ask Dr. Wagman to come and comment.
19 I believe our best data to address that is probably
20 study 289.

21 DR. WAGMAN: Study 289 looked at a
22 population of individuals who were pretreated with

1 a bisphosphonate, which is a common clinical
2 scenario, as you were alluding to. They were
3 required to have been on a bisphosphonate for at
4 least 3 years, and in that year prior to
5 enrollment, 1 or more years of alendronate therapy.

6 At that point, they were transitioned to
7 either alendronate or romosozumab -- I'm sorry,
8 teriparatide or romosozumab, and again, a scenario
9 where they're still at high risk for fracture and
10 still need a bone-forming agent.

11 In the data from 289, what we were able to
12 see was that there were greater gains in bone
13 mineral density -- slide up -- in those individuals
14 who were treated with romosozumab versus those
15 treated with teriparatide.

16 This is a common situation that has been
17 reported in the literature, showing that there may
18 be a bit of a delayed response in patients who have
19 been pretreated with the bisphosphonate, who then
20 transitioned to teriparatide, and in fact, that is
21 what we saw in this study.

22 DR. ORZA: Can I follow up?

1 DR. LEWIS: Yes.

2 DR. ORZA: So those results relate to bone
3 mineral density, but how about fractures or some of
4 the patients' outcomes like pain or functional
5 status or quality of life?: Do you have anything
6 on whether it improves those, either on its own or
7 relative to the teriparatide?

8 DR. WAGMAN: In study 289 -- and we'll keep
9 the slide up, please -- it is a 1-year study. We
10 did not look at fracture outcomes, but what we do
11 have is another estimate of bone strength, and
12 that's using a technique called FEA or finite
13 element analysis.

14 It is a good predictor. It correlates well
15 with fracture strength, or I should say bone
16 strength and anti-risk, reduced risk for factor,
17 and you see that it tracks very nicely with what we
18 see with the results in BMD, greater estimated
19 strength by FEA with romosozumab compared with
20 teriparatide.

21 In this 1-year study, we did not assess
22 patient outcomes such as quality of life for pain.

1 DR. LEWIS: Thank you. Dr. Nahum?

2 DR. NAHUM: Yes, thank you. Dr. Nahum. I
3 have a question for mostly FDA here. It seems to
4 me that the points that were made by the public
5 speakers, and were made by the sponsor this
6 morning, and also FDA, that there's not very much
7 uncertainty around the efficacy piece of this
8 product. There's much more uncertainty around the
9 cardiovascular risk, but I would ask this.

10 We're ultimately going to have to integrate
11 and compare apples with oranges, and I mean that on
12 the efficacy side versus the cardiovascular risk,
13 potentially on the risk side. Have we or should we
14 obtain any sort of value information from patients
15 themselves?

16 On the one hand, we're trading major
17 morbidities and mortality, perhaps, on the fracture
18 side associated with hip fracture with major
19 morbidities and mortality on the risk side. And
20 it's unclear to me, especially listening to the
21 public speakers, which has more weight and which is
22 more valued by patients themselves.

1 There are multiple ways to approach this. I
2 think EMA has many different frameworks that
3 they're working with now that integrate
4 benefit-risk that FDA has not yet adopted and FDA
5 has different mechanisms.

6 But looking at patients and their values as
7 to what they would like to see in their lives,
8 there are other techniques. There are conjoined
9 analyses or other sorts of ways to get at this
10 information. It seems to me that we haven't
11 incorporated that yet, that it hasn't been brought
12 into the discussion, but I think it's critical.

13 Once the integration of the risk-benefit is
14 performed, in whatever sort of framework you care
15 to do it, you have to assign values to these
16 various outcomes and what patients themselves
17 value, more or less, to be able to decide whether
18 this product should or should not be approved in
19 its current form with the currently available data.

20 DR. JOFFE: This is Hylton Joffe. Yes, we
21 have a strong interest in patient-focused drug
22 development. I think one challenge is some of the

1 subjective aspects to assigning value to each of
2 these outcomes. For example, if you have a silent
3 MI, your quality of life's going to be very
4 different than if you have a huge MI or if you have
5 a stroke that leaves you with minor residual
6 deficits versus a devastating stroke.

7 So it's hard to capture the full spectrum of
8 all these things when you're trying to weigh these
9 benefits and risks.

10 DR. WASSERMAN: If the sponsor could also
11 just make a comment? I know that during the FDA's
12 presentation, there was a question over
13 benefit-risk and whether we should be looking at
14 1 versus 3 years.

15 Slide up. We think it's really, really
16 important that when considering benefit-risk, that
17 one looks at a longer duration than just 1 year.
18 So looking at 1 year, I'm going to use an analogy,
19 and forgive me for those of you that still have
20 college loans. But you can imagine -- sorry; I saw
21 the visible sigh -- doing a cost-benefit analysis
22 of what college was like as soon as you graduate,

1 which obviously you've spent a lot of money, but
2 you haven't gotten any of the benefits, versus
3 waiting a few decades until after college.

4 So looking at 1 year, where you get the full
5 risk but a fraction of the benefit, really isn't
6 appropriate. And really, we need to be looking at
7 longer terms. So I would encourage us, as we think
8 about the benefit-risk, to keep an open mind over
9 this and really consider how the benefit,
10 particularly as it relates to reduction in clinical
11 fractures, accrues over time. Thank you.

12 DR. LEWIS: Thank you. I have a question,
13 and then we'll go to Dr. Wang. My question relates
14 to the populations that have been studied.
15 Obviously, both studies that we've looked at have
16 been huge. However, only a very small proportion
17 of the population came from the United States.

18 To what degree do the cardiovascular risk
19 factors -- how similar or different are those
20 cardiovascular risk factors to a United States
21 population? I was going to ask the FDA.

22 DR. KEHOE: I think what we see is when you

1 look at the cardiovascular worldwide risk and
2 things like that, that U.S. is sort of middle of
3 the road compared to Eastern Europe, on one side of
4 potentially higher risk, versus Asia, potentially
5 lower risk.

6 I think it's much more difficult from a
7 cardiovascular perspective than it was for bone
8 mineral density in the osteoporosis perspective,
9 where we could clearly see that the BMD changes
10 across the various regions were the same. We're
11 not sure how to do that necessarily with the
12 regional differences, the worldwide differences.

13 DR. LEWIS: Sure. I didn't mean what was
14 observed in the study; I mean in the whole
15 population. Thank you.

16 DR. WASSERMAN: Dr. Lewis, Dr. Roe can
17 comment on that.

18 DR. LEWIS: Okay.

19 DR. ROE: I think in cardiovascular outcomes
20 trials that are dedicated studies, we see typically
21 that patients enrolled in the United States have a
22 higher risk than those enrolled in other countries,

1 but that doesn't apply to this population.

2 We're talking about postmenopausal women
3 with osteoporosis and what is the distribution of
4 cardiovascular risk factors, and what is the
5 cardiovascular risk by region. There really are no
6 very good global epidemiologic data to really
7 answer that question across different regions of
8 the world. There are data from the United States,
9 as was shown in Medicare, but trying to compare
10 that to other regions of the world are difficult.

11 Sorry. In clarification to your question,
12 is it a question of the population difference or
13 population of those patients who are enrolled in
14 clinical trials?

15 DR. LEWIS: It was the population in
16 general, and that's who would be eligible to use
17 the drug.

18 DR. ROE: That's a very tough question to
19 answer. I just don't think there are comparative
20 epidemiological data.

21 DR. LEWIS: Good data. Thank you.

22 Let's go with Dr. Wang, please, and then

1 we'll go with Dr. Suarez-Almazor.

2 DR. WANG: Thanks. I also had a
3 benefit-risk question. On the sponsor slide CI-7,
4 I think it was one of your introductory slides.
5 Exactly. If the drug were to be approved with a
6 the black-box warning, my question relates to how
7 you would frame this warning.

8 Your proposal here, the first bullet point,
9 seems reasonable. It's the second bullet point
10 that I wanted to ask about. It seems like the
11 benefit-risk should be considered in all patients,
12 not just patients with prior MI or stroke. And in
13 fact, I would go on to ask whether you consider
14 patients with prior MI to stroke to be a population
15 who you would relatively contraindicate for this
16 drug.

17 In other words, should you consider avoiding
18 this drug in those patients? And secondly, there's
19 a broader population of patients at high risk for
20 cardiovascular disease, but who may not have had
21 prior MI or stroke.

22 So again, if you were to go the direction of

1 a black-box warning, if that's what the FDA
2 permitted, should not the second bullet point be
3 broader?

4 DR. WASSERMAN: Thanks, Dr. Wang. So I'm
5 going to call Dr. Sabatine to talk a little bit
6 more about the gradations. But the way that we've
7 approached this, at least when we've gone through
8 our benefit-risk assessment, particularly as it
9 relates to study 142, which we think is a
10 conservative or potentially a worst-case scenario,
11 we deem the benefit-risk at 3 years to be
12 favorable.

13 The reason to point out the patients with a
14 history of myocardial infarction or stroke is, once
15 you become that type of secondary prevention
16 patient, as you well know, your risk basically
17 stays, on average, at about 3 percent a year,
18 versus someone who doesn't have that, it's about
19 1 percent.

20 No matter how many cardiovascular risk
21 factors you pile on to that, it's very hard to get
22 someone who has never had a heart attack or stroke

1 to have that same 3 percent per year.

2 Slide up. What we showed -- and this is
3 where I think it deserves a lot more
4 attention -- is really that first year after the
5 myocardial infarction and stroke when your risk is
6 the highest. It is that period of time where
7 patients have the highest risk of having a MACE
8 event. During that period of time, we think that
9 caution should be taken in those patients,
10 particularly given that the risk is 2 to 3x. Once
11 you get past that 1 year, you basically stay stable
12 at about 3 percent.

13 Dr. Sabatine?

14 DR. SABATINE: Yes. It's a very important
15 question. If you think about wanting to minimize
16 any potential absolute risk increase, then the two
17 things to think about is there a subpopulation
18 that's at higher relative risk, who we've looked
19 through in the subgroup findings, and both we and I
20 think the FDA came to similar conclusions, there
21 wasn't any subgroup where there was a higher
22 relative risk.

1 So really, the only dial to tweak then is
2 the baseline risk. And if that's the case, in the
3 benefit-risk analysis that Dr. Wasserman showed,
4 you can recall that over 3 years, there are about
5 30 fractures prevented, about half as much in terms
6 of hip fractures, 14 or 15. Then for the MACE end,
7 there were maybe 4 MACE, 2 overall CV.

8 That was in this population, which, by and
9 large, didn't have prior MI or stroke. There was a
10 very tiny subset. So that gives you a sense for
11 the world of women with osteoporosis you might
12 treat if you're having a ratio there, at least for
13 hip fracture, that's fourfold more hip fractures
14 prevented than potential MACE cause, and then for
15 all fractures, the multiple would be 7 or 8, or
16 something like that.

17 To the point raised, then if you say, well,
18 now they have a history of MI or stroke, that does
19 kind of move you up I think a step, as you well
20 know, and kind of takes you from maybe 1-
21 ish percent per year to more like the 3 percent, as
22 you see in both these data sets.

1 At that point, still the overall fracture to
2 MACE is still quite favorable. The hip fracture to
3 MACE is still favorable, but gets to be a bit
4 closer. Then, once you get to individuals who are
5 within the first year, now their event rate is
6 3 times higher, then that may be a trade-off.

7 I think as we heard from some of the public
8 comments, that's where you really need to pause and
9 have a very careful conversation. As you point
10 out, for every medicine, there's always going to be
11 a conversation. But where I think, in the low
12 risk, those without prior MI or stroke, the ratio
13 is, at least from my take on the data, so
14 favorable, I don't think that'd be a very long
15 conversation. For those who have had a recent MI
16 or stroke, that's a longer conversation.

17 DR. LEWIS: Thank you. Dr. Suarez-Almazor,
18 and then Dr. Bauer.

19 DR. SUAREZ-ALMAZOR: I have a question for
20 the sponsor and another one -- well, for the FDA;
21 for the sponsor, the second one. The first one
22 relates to what you had in the warning that you

1 were planning, and this is for previous MI or
2 stroke, so basically previous cardiovascular
3 disease risk.

4 However, when we look at the data that was
5 stratified by the FDA, when we look at those that
6 were 75 and older, there's exactly the same risk,
7 both absolute and relative, which is unfortunate
8 because 75 and older are the people who fracture
9 more, but that's not in the warning, and it's
10 actually exactly the same increasing risk as for
11 cardiovascular disease.

12 DR. WASSERMAN: Yes. I'd like to ask
13 Dr. Sabatine. I think the challenge that you're
14 seeing is the challenge of taking a data set that
15 is small in number and then doing subgroup
16 analyses, but I'll ask Dr. Sabatine to comment.

17 DR. SABATINE: Yes. My comments here would
18 be brief. I think, as Dr. Wasserman noted, there
19 are many ways to try to cut the data set. You're
20 still left with the same pie of relatively few
21 cardiovascular and particularly MACE events.

22 I think although age and other risk factors

1 obviously do associate with the risk of
2 cardiovascular disease, that's why they're risk
3 factors, end of the day, it's hard to beat actually
4 having had a history of MI or stroke. So at least
5 from the cardiology perspective, that for us is a
6 very easy cleavage plane. That's clearly a group
7 that's at much higher risk.

8 So an elderly individual without a history
9 of MI or stroke; it's very hard for them to
10 approach that same level of risk. I'd be careful
11 within this data set, where you're having in one
12 trial 60 events to try to parse out that risk. But
13 from larger cardiovascular studies, that step
14 function, I think, is quite clear.

15 DR. WASSERMAN: One last thing to note is,
16 we all kind of find it remarkable when we look at
17 study 337 and 142 and the Medicare database. These
18 women are, on average, 70 to 75 years old. The
19 fact that only 5 percent of them have had a prior
20 MI or stroke, I actually find to be amazing. I
21 would have expected it to be much higher, and
22 that's in the postmenopausal osteoporosis

1 population.

2 DR. SUAREZ-ALMAZOR: That would actually
3 then point to the need of maybe saying that those
4 who are 75 and older are at higher risk because
5 they didn't seem to have a prior MI, and the data
6 here in this particular trial shows that, that they
7 are at a high risk.

8 But anyway, that can go to the discussion.
9 I was just wondering what your thoughts were for
10 not including that.

11 DR. WASSERMAN: I just want to clarify just
12 briefly. Again, we're talking about 60 events per
13 study, 122 when you do the meta-analysis, and we're
14 talking about a potential risk. We have one study
15 that has no cardiovascular risk, and then we have
16 another study where there's an imbalance in events.
17 So I think we're left with some uncertainty.

18 DR. SUAREZ-ALMAZOR: Can I ask the other
19 question that I have for the FDA or for you? But
20 anyway, if I could get the graph 29 from the FDA,
21 slide 29, time to first MACE? I think one of the
22 issues here that worries us is of course the

1 alendronate and what's going on with that,
2 especially if there is another study that
3 eventually might be proposed with alendronate. And
4 if that's not resolved, we may end up with the same
5 issue all over again.

6 One of the questions that I had was if we
7 look at the nonlinear line that the alendronate
8 patients have -- I'm assuming this is intent to
9 treat, and we know that patients notoriously tend
10 to stop oral bisphosphonates after a year or so.

11 So I was wondering if there was an effect of
12 adherence maybe on that second year on the
13 alendronate that could perhaps take away from any
14 protective effect that alendronate may have because
15 patients may not have been adherent on the second
16 year within the trial. I don't know if you have
17 that data or not.

18 Then I think this was mentioned before also
19 on the upper curve, I don't see the effect of
20 alendronate being protective, starting at month 12,
21 which is also unexpected. But with respect to
22 adherence, were you able to see if there was an

1 effect of nonadherence on the second year, on the
2 alendronate group?

3 DR. WASSERMAN: There's no evidence that we
4 have that there was an issue of nonadherence
5 contributing to that. In fact, slide up, we did an
6 analysis -- because of the nonlinear effect, we did
7 a landmark analysis. A landmark analysis is an
8 analysis where, at a certain period of time,
9 everyone that has not had an event is basically
10 included.

11 So we got rid of the first 3 months of
12 study 142. And you'll see that by getting rid of
13 the first 3 months -- so now you have 9 months of
14 treatment on romosozumab -- at the end of the
15 overall study period now, the hazard ratio is
16 basically 1.

17 So again, we're dealing with small numbers
18 of events, but it does call into question the
19 behavior of the alendronate, as Dr. Sabatine has
20 noted and as the FDA noted. It is what it is. It
21 leaves us with some uncertainty. That being said,
22 the benefit that we've seen is very, very clear,

1 and there's no uncertainty around that.

2 DR. LEWIS: Thank you. Dr. Bauer and then
3 Dr. Adler?

4 DR. JUNG: Before your question, FDA wanted
5 to add a note for the figure 29. So if you look at
6 the figure 29, the number of patients will still be
7 followed, but it's small, as seen by the number of
8 patients at risk in the table.

9 Can you pull up the figure? No.
10 Dr. Karp's, page 29.

11 What you see in the right figure, you can
12 see the number of patients that will still be
13 followed is small. Compared to the beginning, it's
14 2,040 versus 200 something, the patients number at
15 risk.

16 Also, I want to point out, from the 12-month
17 study double-blind period, it's difficult to
18 discern in this figure, but if you look at the
19 dotted line of the study 142 in the alendronate
20 group, you can see a long plateau in the beginning
21 for certain days. The first alendronate event
22 occurred in days 87, and before that event, in the

1 romosozumab group, there were 12 more MACE events
2 before the alendronate group starts MACE events. I
3 just want to add that comment.

4 DR. WASSERMAN: Just to clarify, we've
5 truncated our analyses at month 36, where basically
6 that's the median. So at 239 and 242, where we
7 haven't used any of that data, where it's just
8 one-tenth of the population, we've stuck to
9 everything where we've had at least 50 percent of
10 the data.

11 DR. JUNG: Yes. I want to also note that
12 the subsequent number at risk is from your
13 sponsor's data?

14 DR. WASSERMAN: That's correct

15 DR. LEWIS: Thanks. Dr. Bauer?

16 DR. BAUER: Thank you. I want to make a
17 comment and then ask a question of both the sponsor
18 and the FDA. And while we're waiting, can you get
19 the sponsor slide CR-9 to pull up, please?

20 My comment has to do with this notion of the
21 cardioprotective effects of alendronate or
22 bisphosphonates in general or not. This has really

1 been a very active area of investigation, and, in
2 fact, even back in the '90s, when we did the
3 fracture intervention trial, we actually went back
4 and did a blinded analysis. There was no evidence
5 of ischemic events, and I believe that data was
6 eventually submitted to the FDA.

7 If you don't believe me, there was actually
8 a very large meta-analysis published in PLOS One in
9 2015, 58 bisphosphonate trials, again, specifically
10 looking at the effect of bisphosphonates in
11 ischemic heart disease, and it was a null result.

12 The business about nonlinearity, if there is
13 a protective effect early in the trial, and the
14 overall effect is no, that must mean that there is
15 an adverse effect later in the trial. And again,
16 that just hasn't been seen. So I think, from a
17 Bayesian standpoint, I just think it's really,
18 really unlikely that that accounts for the
19 observation that we've seen in these studies.

20 My question has to do with this slide, and
21 it has to do with what are the implications of the
22 follow-on study, and how will, first, the sponsor,

1 but also important, the FDA interpret the results
2 of a follow-up safety trial? Because it's not
3 clear to me how that is going to change the
4 fundamental discussion, which I see in this trial,
5 in this slide right here, which as a practicing
6 clinician, if I'm going to advise the patient about
7 what are the risks and benefits about taking this
8 medication, I'm going to probably want to focus in
9 on both the hip fracture data absolute risk as well
10 as the MACE absolute risk.

11 Although I would take some exception to what
12 one of the sponsors said, that there appeared to be
13 an over -- at least in terms of hip fracture, I'd
14 argue that these are actually on the same order of
15 magnitude; that is 14 hip fractures prevented and
16 approximately 9 MACE events caused.

17 Someone did bring up the evidence about how
18 various hip fractures are weighed and their impact
19 on quality of life as well as disability. This has
20 been looked at quite extensively in observational
21 studies, and there's no question that hip fractures
22 have a profound effect on quality of life. In

1 fact, it equals or approaches that seen with severe
2 cardiovascular events as well.

3 But my question, more fundamentally, is how
4 would a follow-on study change this fundamental
5 dynamic? I'm sitting with a patient saying, well,
6 if you take this medication for a year, we think
7 that 14 hip fractures will be prevented in a
8 thousand women, but we think we may cause 9 MACE
9 events. And it's not clear to me how an
10 observational study that's powered for a relative
11 risk of 2 -- I believe is what you said, which I
12 believe is more or less what's in this risk here,
13 in 142, the relative risk of approximately 2 for
14 MACE -- how that's going to change that fundamental
15 discussion.

16 DR. WASSERMAN: Sure. Let me just try to
17 first address this slide, and you can fault the
18 sponsor for this. But we stuck with study 142
19 where the signal was seen to produce this.

20 DR. BAUER: Right. Understood.

21 DR. WASSERMAN: I think the totality of the
22 data would suggest that the hazard is probably

1 closer to what we saw in the meta-analysis based on
2 all of the extensive work we've done. But what's
3 important to note on this is we did put the
4 95 percent confidence intervals, which are quite
5 wide, so it goes from basically rather than causing
6 9 MACE, actually preventing 6, to causing 25.

7 So there's a lot of uncertainty here. We
8 personally think that the meta-analysis is a more
9 accurate representation. Slide up. The
10 meta-analysis here, you can see that it's 4 MACE
11 versus 14 hip fractures.

12 Just to kind of put this in context, the
13 event rate that was in 142, if I remember
14 correctly, on average, is about 5 to 6 percent MACE
15 events per 3 years. In the meta-analysis, when we
16 look at that, it's about 3 and a half to 4 and a
17 half percent. So that difference -- and this is
18 what we've been discussing right now. That
19 difference in terms of the event rate is what takes
20 you from the 9 to 4 and decreases the confidence
21 intervals as well.

22 DR. BAUER: Okay. But the upper limit of

1 that confidence interval is 11 --

2 DR. WASSERMAN: It still is, yes.

3 DR. BAUER: -- suggesting that, again, if
4 you take the best -- or the point estimate for hip
5 fractures are 14, compare that to 11 MACE events at
6 worst-case scenario, which I grant you is probably
7 not the most likely, that's not a very easy
8 conversation to have in terms of risk-to-benefit
9 with an individual.

10 DR. WASSERMAN: I think if we're going to be
11 fair, we'd compare the 11 to the 24. But you're
12 right, this is challenging.

13 DR. BAUER: So importantly, tell us about
14 the follow-on study and how you think that would
15 change that fundamental dynamic with an
16 observational study, for example, or with a more
17 randomized trial?

18 DR. WASSERMAN: Can I have CR-9? The
19 purpose of us doing an observational study is we
20 want to assure ourselves -- slide up -- that the
21 MACE event that was seen in study 142 -- where that
22 increased relative risk had a hazard ratio of about

1 1.87, the FDA noted that the hazard went up to
2 about 3 -- we think that observational study can
3 address that.

4 We can look at that. We can monitor the
5 incidence in patients receiving romosozumab in the
6 United States, reflecting the diversity of the
7 population in a way that would address this
8 concern. We can do it expeditiously. We can
9 iterate on it as we go along, as we'll be
10 continuing to accumulate data, and we really want
11 to partner with the FDA to make this as robust and
12 as informative as possible.

13 DR. LEWIS: Thank you. We have time for two
14 more clarifying questions, clarifying questions
15 only, and then we'll do the discussion, one from
16 Dr. Adler and one from Dr. Gerhard.

17 DR. ADLER: Adler. In terms of the
18 surveillance study, I'd like to learn from history,
19 and I'm really concerned about having a black-box
20 warning about patients at very high cardiovascular
21 disease not being good candidates for romo, and
22 then doing a surveillance study.

1 So we have another anabolic agent called
2 teriparatide, which is not to be used in patients
3 who are at higher risk for osteosarcoma. So those
4 with Padgett's disease, for example, or who have
5 had radiation to bone are not supposed to get this.
6 And the surveillance studies so far show that
7 there's no increased incidence of osteosarcoma, but
8 the population that's likely getting these drugs
9 has already had those at highest risks eliminated.

10 So I'm concerned that if the black-box
11 warning says those at highest risk for MACE should
12 not get not get this drug, then a surveillance
13 study may or may not be able to help us.

14 DR. LEWIS: Did you have a question there or
15 just wanted to comment?

16 DR. ADLER: A comment.

17 DR. LEWIS: Thank you.

18 DR. WASSERMAN: If we can respond to that,
19 we thought a lot about that. Dr. Roe?

20 DR. ROE: I think that gets to the
21 fundamental question of what would a surveillance
22 study be intended to address, recognizing that only

1 5 percent of the population has a history of prior
2 MI or stroke, and there's an unmet need in
3 osteoporosis as we've clearly heard. When this
4 drug is used in practice in the diverse U.S.
5 patient population, is there a potential CV risk?

6 If there is a black-box warning, will
7 providers use it in those patients or will they
8 not? That's uncertain, as we talked about earlier
9 this day. So the idea is in real time, with high-
10 quality methods, with partnership with the FDA,
11 based upon previous experience with such types of
12 studies, I believe that risks can be assessed
13 accurately and with the proper methodology in the
14 patients in whom it will be used.

15 Will it answer the question of those with
16 prior MI or stroke? It depends on how it's used,
17 but I think in the much broader population where
18 there is 95 percent of the patients who don't have
19 that prior history, I think that's an important
20 question that a surveillance study can address.

21 DR. LEWIS: Thank you. Dr. Gerhard?

22 DR. GERHARD: My point is also more in

1 response to some comments, so I'd be happy to make
2 it in the next session if you'd prefer.

3 **Questions to the Committee**

4 **Discussion and Voting**

5 DR. LEWIS: I think that's fair because I
6 think at this point, people do have more discussion
7 points than they do actual clarifying questions.

8 So I know that there's a break in the
9 agenda, but we're going to forego that because I
10 think that we want to be sure that all the panel
11 members have an opportunity to vote. I know some
12 people are needing to make travel arrangements.

13 So the chair and DFO of an advisory
14 committee are encouraged to generate a robust
15 discussion. At this point, we're going to proceed
16 with the questions to the committee and the panel
17 questions. I'd like to remind the public observers
18 that while this meeting is open for public
19 observation, public attendees may not participate,
20 especially except at the specific request of the
21 panel.

22 I think we're going to pull up the

1 questions. So we'll go through each question.

2 First question is only for discussion.

3 Discuss whether the cardiovascular safety of
4 romosozumab has been adequately characterized. If
5 additional safety data are needed, discuss the
6 types of data that are needed and whether these
7 data should be obtained pre-approval or
8 post-approval.

9 Is this question for discussion clear for
10 the panel?

11 (No response.)

12 DR. LEWIS: I'm going to just open it up,
13 and we'll take names appropriately. Dr. Gerhard
14 wants to start. I'm going to let him start.

15 DR. GERHARD: Thank you very much. I think
16 the answer to the initial question is very clear in
17 that it has not been adequately characterized;
18 otherwise, we wouldn't have this discussion back
19 and forth. And I would argue that we put in this
20 discussion about benefit-risk, a little bit the
21 cart before the horse.

22 What we have, really, is a situation where

1 we have two studies that were not powered for
2 cardiovascular outcomes that have conflicting or
3 seemingly contradictory findings. However, when we
4 look at the confidence intervals, they clearly
5 overlap. We can argue about the exact way to look
6 at this statistically, but in totality, the data's
7 probably compatible with the drug not having a
8 risk, or meaningful risk, and a risk that's maybe
9 twofold, maybe even a tad higher. We just don't
10 know at this point.

11 That makes any discussion of benefit-risk
12 really difficult because it matters, when we look
13 at these confidence intervals, whether we do it on
14 absolute or relative scales at the lower or higher
15 spectrum. The approach here that's taken is a
16 little bit to say we restrict the population
17 through the labeling to one that is likely to
18 derive the highest benefit, that's at highest risk
19 for fracture, and potentially restrict by excluding
20 people at highest cardiovascular risk to make sure
21 that the benefit-risk balance is positive.

22 But with the current level of information or

1 data, we make a mistake in almost any scenario. We
2 either, if we are at the high end of the
3 cardiovascular risk of these estimates, maybe
4 expose people to a negative benefit-risk because
5 they actually have a higher cardiovascular risk in
6 comparison to the benefit.

7 On the flip side, on this, I would argue, in
8 considering kind of what can be done to improve
9 this, and maybe as a carrot for a sponsor, there's
10 also a significant risks that we create a labeling
11 or a situation where situation where we actually
12 withhold this drug from a lot of people that would
13 benefit from it if in fact the true cardiovascular
14 risk is at the low end of the spectrum or maybe
15 even doesn't exist at all.

16 So in other words, we just need more
17 information to quantify the cardiovascular risk,
18 not just answer the question, does it exist or not,
19 but see how big is it and put a confidence limit
20 that is actionable and that's not in relative terms
21 from 1.0 to 3.

22 This is further complicated when we look at

1 absolute risk and different populations and so on,
2 but first we have to quantify the risk. And I
3 believe the only way to do this is to have a
4 randomized study. That's what I do for a living.
5 I don't see any observational approach to have a
6 credible result that gives more clarity on the
7 cardiovascular risk associated with this drug
8 because of this extreme channeling.

9 In my opinion, this could be done
10 post-approval, and I would encourage FDA and
11 sponsor to think about innovative approaches that
12 maybe stop short of a traditional cardiovascular
13 outcomes trial, which might be cost prohibitive and
14 would take too long, and try to find a way to do a
15 pragmatic trial that has baseline randomization
16 that uses a lot of the methodology using existing
17 databases with electronic health record review or
18 medical record review, and try to find a way to get
19 to the level of certainty about the cardiovascular
20 risk that we need.

21 DR. LEWIS: Thank you. Dr. Lincoff?

22 DR. LINCOFF: Again, I agree that it has not

1 been adequately characterized, and that's why we're
2 here. I do clinical trials for a living, but I do
3 respect the idea that this may be difficult to do
4 another randomized trial. I believe the benefit is
5 unequivocal, and I don't think equipoise will exist
6 if this drug is approved regarding efficacy.

7 So I think it will be very difficult to do a
8 simple trial such as PCORI has done with aspirin,
9 for example, because there is true equipoise in the
10 efficacy with different doses of aspirin.

11 But I think that it is still an important
12 question to characterize what is the magnitude, if
13 any, of the cardiovascular risk because I think
14 there's a very good possibility there's none at
15 all. It could well be zero.

16 The striking thing is the relative risks
17 don't seem to vary as much among different
18 populations, whereas of course the absolute risk
19 does depend upon the baseline. So I think we can
20 gain important information, even with excluding, at
21 least temporarily, for a period of while we're
22 trying to assess, those patients who are at the

1 highest risk; that is, those who have had a recent
2 myocardial infarction or stroke. And again, that's
3 a temporary situation. That doesn't bar them
4 forever from receiving the drug.

5 I think a post-approval study is appropriate
6 because I don't think withholding this therapy for
7 the years that would be required to study this is
8 warranted. But I think that the passive -- we use
9 databases -- and various types of existing data
10 that's passively collected will be sufficient.

11 I think we need a detailed enough data set,
12 a granularity of data, that allows us to make
13 comparisons between patients who are and are not on
14 this therapy but have the diagnosis, and that allow
15 the propensity matching and elimination of the
16 patients at the extremes who aren't comparable
17 between the groups.

18 I think that granularity only can be done
19 with registries. I think that the sites that have
20 the specialists that are going to be prescribing
21 these kind of medications can enroll in registries
22 where they agree to enroll all their patients who

1 are treated with this agent or with comparable
2 agents, and with enough granularity of data,
3 focusing on what we think are important predictors,
4 to try to tease out in the end of analysis that
5 allows a reasonable adjusted analysis and
6 assessment of what the risk is.

7 Clearly, a randomized trial would be the
8 best way to get this information, but I think given
9 the lack of other products that have this sort of
10 efficacy which differentiates it from, say, the
11 diabetes market where we have to do post-approval
12 cardiovascular safety studies -- but we can justify
13 that because we have other agents right now to
14 treat that or even for obesity.

15 I think given the lack of other agents with
16 this sort of efficacy, that the ideal of a
17 randomized trial -- although, again, the ideal, I
18 think there are alternatives, but I don't think
19 they're the sort of passive data collection that
20 had been advocated.

21 DR. LEWIS: Thank you. Dr. Braunstein?

22 DR. GERHARD: Thank you. Just a very quick

1 follow-up. Didn't we just hear that there is a
2 population where there is equipoise, not in terms
3 of the efficacy alone, but in terms of efficacy and
4 risk for the population, where it's not clear
5 whether the benefit outweighs the cardiovascular
6 risk?

7 We just had Dr. Bauer making this comment
8 that there would be osteoporosis patients with a
9 lower risk and maybe somewhat higher; that there is
10 a population where currently there is equipoise.

11 DR. BAUER: I'm not sure I'd argue for a
12 placebo. I don't think there's equipoise for
13 placebo.

14 Is that what you're referring to? No. I
15 guess I would argue that there's equipoise for
16 other active agents. For example, a long-acting
17 bisphosphonate, you could do a comparative
18 effectiveness study where you're looking at the
19 cardiovascular outcomes compared to a single dose
20 of a long-acting bisphosphonate with cardiovascular
21 outcomes. I think that would be totally defensible
22 from an ethical standpoint.

1 DR. LEWIS: Thank you. Dr. Braunstein?

2 DR. BRAUNSTEIN: Braunstein. I'm very
3 comfortable with what's been done so far with
4 recommending approval for the drug with the
5 black-box warning and a contraindication for
6 somebody who's had a stroke or an MI in the
7 previous year. Having said that, I'd be
8 comfortable with an observational study as proposed
9 by the sponsor, although I agree that a registry
10 study would be even better.

11 I would like to see another study done,
12 after approval, looking at, in a randomized
13 fashion, high-risk patients who are treated with
14 rozo versus alendronate if placebo is felt to be
15 not an appropriate substitute because of the
16 severity of osteoporosis. I would like to see that
17 done to try to see if there is, indeed, increased
18 cardiovascular risk after a year of rozo therapy in
19 comparison to either comparative control or
20 preferably a comparator control as well as a
21 placebo.

22 In addition, as part of that study, I'd like

1 to see coronary CT data or coronary angiography
2 before and after a year, and carotid intimal
3 thickness studies before and after a year in order
4 to see if there's any progression of
5 atherosclerotic plaques in the coronary arteries or
6 the carotid arteries on the therapy versus the
7 comparator or the placebo.

8 DR. KEHOE: Can I ask a clarifying question
9 of Dr. Braunstein?

10 Dr. Braunstein, you were talking about high
11 risk, that you would like to see this study in
12 high-risk patients. Which high-risk,
13 cardiovascular or osteoporosis?

14 DR. BRAUNSTEIN: High-risk cardiovascular
15 patients with osteoporosis, with significant
16 osteoporosis.

17 DR. LEWIS: Thank you. Ms. Portis?

18 MS. COMPAGNI-PORTIS: I do agree that the
19 need is high and that there's some efficacy here
20 that's of significance, but I really don't think we
21 have a deep enough understanding of the safety
22 issues. The problem is I don't feel like we really

1 know the who or the why of what the risk is, and we
2 don't know that in the U.S. population.

3 As Dr. Shaw brought up before and we keep
4 coming back to, I think the problem with the
5 black-box warning is that will keep us from getting
6 some of the information that we need.

7 I'd like more study to happen pre-approval.
8 I really think it behooves us as a committee and
9 for FDA to make sure, prior to approval, that we
10 understand the risk. One of our speakers brought
11 up the precautionary principle, and I have to say I
12 think that's important. It's like, let's find out
13 first. Yes, this may be a really important
14 treatment, but I'd rather that we didn't lose
15 people along the way of figuring this out.

16 DR. LEWIS: Thank you. Dr. Shaw?

17 DR. SHAW: Yes. I did want to echo some of
18 the statements being made earlier. I agree. I
19 don't think we've adequately characterized the
20 cardiovascular safety, and I really think we can't
21 reliably answer this with an observational study
22 unless it's being done at the level of what a

1 clinical trial would do, which is prospectively
2 following people and getting all of their risk
3 factors so we can understand and do an adjustment.

4 If people, post-approval, are just being
5 assigned a drug based on all kinds of factors,
6 about them and their family, et cetera -- I can't
7 imagine a registry -- maybe I'm naïve, but I can't
8 imagine a registry or a passive database that would
9 allow us to do that reliably.

10 I just want to throw out, I don't know if I
11 know the perfect solution, but relying on
12 observational data only post-approval, I don't
13 think is going to help us answer this reliably. We
14 just won't have correct comparisons. We will look
15 at groups of people, but we won't be able to
16 reliably compare them.

17 DR. LEWIS: Thank you. Dr. Orza?

18 DR. ORZA: So I agree that options are good,
19 and that in an ideal context of true shared
20 decision making, with both parties fully informed,
21 that people could make this kind of a trade-off if
22 they had the information. But I think we don't

1 have the information to give them, so I don't even
2 know what those shared decision-making materials
3 could look like. I think the only way to make them
4 more robust is through a prospective randomized
5 trial.

6 What I worry about, in addition to the
7 severe limitations that would come with a registry
8 or an observational study, are that people would
9 not be in a context where they would be watched
10 over carefully enough.

11 So if we think this risk is real, that
12 suggests that there should be a very intense level
13 of monitoring for these cardiovascular side
14 effects, and that wouldn't happen in an
15 observational general practice setting, which is
16 far, far from the ideal.

17 DR. LEWIS: Thank you. Dr. Burman?

18 DR. BURMAN: Thank you. My comments are the
19 following. The cardiovascular signal exists in one
20 study generally within a year, but was not seen in
21 another study, nor at 3 years, and also not in
22 patients with congenital abnormalities since

1 sclerostin, nor in preclinical data.

2 However, I think the question of increased
3 cardiovascular risk is too important to ignore. I
4 recommend, as others did, a postmarketing study.
5 It should be a rigorous cardiovascular outcomes
6 study rather than an observational or registration
7 study, which just have too many problems and
8 fallacies that have been brought out before.

9 We need to definitively answer the basic
10 question, whether this agent increases
11 cardiovascular risk. The study can be a
12 cardiovascular outcomes study for 1 to 2 years, can
13 be enriched with older patients with cardiovascular
14 disease, and can have some of the parameters that
15 Dr. Braunstein just mentioned as well as
16 cholesterol. In the meantime, there should be a
17 black-box warning, as was noted by the company.

18 DR. LEWIS: Thank you. Dr. Wang?

19 DR. WANG: I just want to reiterate the
20 concern raised by Dr. Lincoff and others about the
21 real challenges with performing a cardiovascular
22 outcomes study in this space. I think we all agree

1 that that is the gold standard. It's how we can
2 eliminate confounding. But the traditional
3 strategies to do a cardiovascular outcomes study
4 practically, which we've seen in the diabetes
5 studies, is to enrich the population or to extend
6 the follow-up so you can get your events.

7 Here, we have a drug that is given for only
8 12 months, so extending the follow-up does not seem
9 exactly to fit the therapy. Enriching the
10 population, traditionally done by including lots of
11 people with prior events, is getting us away from
12 exactly the population that we think this
13 medication's going to get targeted at.

14 If you then say, then we'll try to target a
15 population that's very similar to the
16 postmenopausal osteoporosis population in 142.
17 Even if we do a back-of-the-envelope, it's a
18 7 [000] or 8,000-person study that yielded
19 60 events. I think we heard earlier that for a
20 standard cardiovascular outcomes study, we're going
21 from 500 to a thousand events.

22 So you can do the math. You're talking

1 about a study that is just not going to be done.
2 So the issue, if you require a cardiovascular
3 outcomes study, especially pre-approval, is are you
4 willing to risk the chance that you will never
5 offer this therapy to patients?

6 DR. LEWIS: Thank you. Dr. Bauer?

7 DR. BAUER: Wow. That changes exactly what
8 I was going to respond to, but I think I do need to
9 respond to that, which is to say there are no good
10 options here. But I would argue that I am very
11 concerned with a postmarketing study that's of an
12 observational nature that is inconclusive, and what
13 are clinicians and what are regulatory agencies
14 supposed to do?

15 I would argue that, in fact, the drug has
16 unbelievably clinical potential in the osteoporosis
17 arena. There's absolutely no doubt about that; I'm
18 totally convinced of it. The question is how do we
19 reliably counsel patients about the relative risks
20 and benefits, and I am not convinced at all that
21 that can be done, at least rigorously, with the
22 type of rigor that we will need to answer this

1 question with an observational study.

2 Therefore, I'm highly enthusiastic about a
3 postmarketing, post-approval randomized trial that
4 is pragmatic and comparative to another
5 osteoporosis therapy.

6 DR. LEWIS: Thank you. Dr. Blaha first.

7 DR. BLAHA: Mike Blaha. I just wanted to
8 basically go on record agreeing with everything
9 that Dr. Wang said, and I am highly, highly
10 concerned. In fact, I think it's implausible to do
11 a randomized control trial that's powered for
12 cardiovascular outcomes.

13 In terms of that recommendation, potentially
14 doing a head-to-head study with another agent might
15 even be more implausible to do because it might
16 even require more patients once you're comparing
17 the two active comparators.

18 These randomized controlled trials powered
19 for cardiovascular outcomes will be very, very hard
20 to do.

21 DR. BAUER: I meant an active osteoporosis
22 comparator, not cardiovascular.

1 DR. BLAHA: Right.

2 DR. BAUER: But it shouldn't affect the
3 event rate if a comparator has been shown not to
4 influence cardiovascular.

5 DR. BLAHA: If we're sure of that; yes, if
6 we're sure of that. We'll have the same
7 discussions of what the comparator might be doing,
8 though

9 DR. LEWIS: Dr. Khosla?

10 DR. KHOSLA: I just want to kind of
11 emphasize the remarkable skeletal efficacy of this
12 drug. Truly, it's better than anything we've seen
13 before, so I don't want the panel to lose sight of
14 that fact. I think on the flip side, I would agree
15 with Dr. Wang that to really rigorously sort out
16 the cardiovascular effect in RCT is going to be
17 basically impossible.

18 The other thing I think the panel should
19 keep in mind is that this drug is not going to be
20 prescribed by primary care physicians. It will be
21 prescribed by subspecialists, whether it's in
22 rheumatology, or endocrinology, or other people who

1 are really invested in the treatment of complicated
2 osteoporosis patients.

3 So I think it will be much easier to have
4 tracking of these patients than if it were used in
5 a primary care setting as one of many other
6 treatments. So whether it's through an
7 observational study or through more detailed
8 registries, to me, that really is the only viable
9 path forward; otherwise, this drug isn't going to
10 be approved or use. So I think you have to kind of
11 keep that in mind.

12 DR. LEWIS: Thank you. Dr. Suarez-Almazor?

13 DR. SUAREZ-ALMAZOR: Yes. I also think that
14 a clinical trial will basically be impossible if
15 it's done premarket pre-approval. I mean,
16 thousands of patients, years and years, I don't
17 even know that the drug would make it to the
18 market.

19 If it's done afterwards, typically, when we
20 have a cardiovascular outcomes study done after
21 approval of a drug, it's when you've seen a signal
22 in surveillance after the drug is in the market,

1 but usually there's no warning or black-box
2 warning.

3 In this particular case, if it were to be
4 approved, because it would have the black-box
5 warning, it would almost be impossible to convince
6 patients who fall under that warning to participate
7 in the trial. So I don't see how that could be
8 ethical or feasible at all.

9 With respect to the observational study, I
10 was not very clear what the sponsor had in mind. I
11 don't think that a database study that's based on
12 Medicare, or MarketScan, or those kinds of
13 administrative databases would be adequate. I
14 think it should be a prospective cohort study where
15 data is being collected from patients that can
16 provide rich information with respect to
17 cardiovascular risk factors and some other
18 variables.

19 So again, I am not sure what the sponsor had
20 in mind, but I don't think that just using
21 administrative databases or just registering with
22 clinical variables, self-reported by patients or by

1 physicians, would be adequate.

2 DR. LEWIS: Dr. Nahum and then Dr. Gerhard.

3 DR. NAHUM: Yes. Thank you. Dr. Nahum. I
4 have three quick points. The first one is I guess
5 I'm just not completely convinced yet that there's
6 not a high degree of overlap between the high-risk
7 population for fractures and the high-risk
8 population for MACE events. It would seem to me
9 that these run together to some extent, and they
10 have to because they're both dependent on age,
11 mobility, things of this nature.

12 So the idea of parsing this out in labeling
13 so that you, on the one hand, get a high-risk
14 fracture population but a low-risk cardiovascular
15 population doesn't seem, to me, to be completely
16 realistic. It seems like there's going to be a
17 huge amount of overlap here. This will be
18 delegated to the physicians who are doing the
19 prescribing.

20 Clearly, the decision making will be
21 different in different places by different sorts of
22 prescribers, and it doesn't seem as if it will be

1 executable in the way that we would like to imagine
2 it could be only because of the overlap between the
3 two risk conditions. That's part 1.

4 Part 2 is sort of optimistic. I think based
5 on the data that we've seen, if we do have new
6 trial data, however it's obtained, it would appear
7 that we only need 1 year of trial data to be able
8 to see whether or not this increased cardiovascular
9 risk is actually there or not because, in my
10 estimation, looking at the data that's already been
11 presented, that's when it would become apparent.

12 So this really becomes an issue of just
13 recruiting lots and lots of patients and watching
14 them for a year. It's not an issue of following
15 people after 5 or 10 years, which I think is good
16 in principle.

17 But then the last point I'd like to make is
18 I really don't see how it is possible, as other
19 people have mentioned, to put a black-box warning
20 in, to narrow the population that would receive the
21 drug, and then make a reasonable assessment as to
22 whether or not there would or would not be an

1 increased risk of cardiovascular MACE events in a
2 population that's not studied.

3 The only way that you could even imagine
4 approaching that would be able to get very, very
5 granular, very, very specific, and very, very
6 detailed information about all those patients. And
7 as we all know, that's not the kind of data that
8 you obtain typically in observational studies
9 postmarketing.

10 So it doesn't seem to me that you'd be able
11 to get the right data in an observational
12 postmarketing study, although I do agree with what
13 some other people have sort of alluded to, that
14 perhaps it would be possible to both approve the
15 drug and have a postmarketing commitment for
16 another clinical trial that would be randomized in
17 nature to incorporate that high-risk population if
18 you could get those people to enroll. So those are
19 my comments.

20 DR. LEWIS: Thank you. Dr. Gerhard and then
21 Dr. Weber.

22 DR. GERHARD: First, another comment about

1 the observational study; it's not only that we have
2 lack of confidence in these findings of the
3 observational study. We know, for a fact or close
4 to a fact, in which direction the result will be
5 biased. It'll make the drug safer. It'll make the
6 drug look safer.

7 So given that the whole point is to rule out
8 increased cardiovascular risk, to start out an
9 observational study in a fashion that we know will
10 underestimate the risk because it channels the
11 high-risk people away from the drug is a moot
12 point. We'll never get an answer about the
13 cardiovascular risk from an observational
14 post-approval study.

15 The only exception potentially would be if
16 we'd have a prospective data collection in place
17 that has close to perfect ascertainment of
18 cardiovascular risk factors. I'm not talking about
19 just prior stroke events or MIs, but all
20 cardiovascular risk factors.

21 I think that is practically not possible,
22 particularly in the settings that these drugs will

1 be used. These aren't physicians that can apply
2 batteries of cardiovascular tests. I could be
3 convinced otherwise, but I think that's actually
4 the less feasible approach.

5 When we come to the alternative, the trial,
6 I think my point that I was trying to make got a
7 little bit lost. I'm talking about large simple
8 trials. We're talking about cardiovascular
9 outcomes trials here that are much harder to
10 implement.

11 The idea of a large simple trial is, in its
12 extreme form -- and there are gradations of
13 this -- randomization at baseline between drug
14 understudy and a therapeutic alternative, in this
15 case that would treat the osteoporosis. Again, in
16 its extreme form, no follow-up whatsoever; we just
17 look at their Medicare data and see whether they
18 die, whether they get hospitalized for myocardial
19 infarction, for stroke, combinations of this. We've
20 seen their algorithms that have identified these
21 outcomes.

22 The feasibility issues are only in the

1 recruitment of patients and randomizations, which
2 are substantial. I give you that. But in at least
3 one way to implement it, there wouldn't be any
4 other commitment. We could follow patients for a
5 year. We could follow them for 5 years. They will
6 be in the Medicare data. We can follow them.

7 I would just encourage people to think
8 creatively about this and don't make this choice
9 between two infeasible approaches, the
10 observational study that will give you a wrong
11 outcome and the cardiovascular outcomes trial
12 that's not feasible.

13 DR. LEWIS: So I'm confused. So you're
14 saying -- it wasn't clear to me -- a large, quote,
15 "simple" trial, randomizing romo to what, and
16 collecting data through Medicare for cardiovascular
17 outcomes.

18 DR. GERHARD: It's a combination of the
19 approach that combines the randomization as the
20 key, one of the key benefits of the traditional
21 clinical trial, and the data collection is done the
22 way it would be traditionally done for

1 observational studies. In this case, it would be
2 the Medicare population.

3 One example would be the ZODIAC trial for
4 ziprasidone. This was about 10 years ago.
5 Treatment of schizophrenia; ziprasidone had
6 preclinical QT prolongation observed, but it was
7 unclear whether that would confer a mortality risk.
8 I believe Pfizer was the sponsor. It was a study
9 of, I think, 18 [000] to 20,000 patients with
10 schizophrenia, randomized ziprasidone versus an
11 alternative antipsychotic medication, and then just
12 following patients up and observing mortality.

13 So there is a precedent for these types of
14 approaches, and schizophrenia as a trial population
15 is probably as complicated or difficult as this
16 population here.

17 DR. WASSERMAN: Can I ask the chair for
18 permission to respond about the large simple?

19 DR. LEWIS: I have one more clarifying
20 question. So you're saying the romo versus a
21 placebo versus nothing, just put people on romo,
22 and it's not randomized.

1 DR. GERHARD: I'm not a clinician that
2 treats osteoporosis. The most comparable --

3 DR. LEWIS: Some other treatment.

4 DR. WASSERMAN: I'd like to, again, offer
5 some commentary. I am leading a study where that's
6 being done right now, looking at aspirin dose,
7 which is obviously a non-prescribed medication. I
8 believe in the power of randomization. I agree a
9 hundred percent that that can truly equal the
10 playing field.

11 I think the question here is one of
12 feasibility, and what is a large simple trial, and
13 can it really be done in the fashion that you
14 described, and/or could a prospective registry
15 embedded in electronic health record data
16 collection as part of routine clinical care be done
17 to further and more precisely collect baseline
18 cardiovascular and clinical characteristic
19 information? The second part, absolutely that can
20 be done, and certainly that type of study could be
21 described.

22 I think there's some fallibility in this

1 large simple trial approach. Doing a clinical
2 trial with randomization requires the IRB to
3 approve the study, the investigator to approach the
4 patient, the patient to provide informed consent.
5 Then there would be provision of drug and the
6 active comparator.

7 Even follow-up through administrative claims
8 and/or through electronic health record data is not
9 simple, and we're experiencing that right now in
10 the ADAPTABLE trial, and I'd be happy to share more
11 detailed information at your discretion about that.

12 So I'm a huge believer in large simple
13 trials, but the mechanics of doing that are not so
14 straightforward. I hear equipoise among the
15 committee members about what type of study could be
16 done, but I believe there are a lot of options
17 beforehand that the FDA could consider to design
18 the best study to answer the question at play, but
19 recognizing there are limitations with all those,
20 and doing a randomized controlled trial is never
21 simple.

22 DR. LEWIS: Thank you. Dr. Weber and then

1 Dr. Edwards, who's on the phone.

2 DR. WEBER: Thank you. This is Tom Weber.
3 Before I have some comments about a discussion
4 question, I want to respond to Dr. Gerhard. I
5 think that the feasibility of doing such a trial
6 that you suggested is difficult, and the very
7 reason is many of these patients who were starting
8 these therapies have not tolerated or cannot take
9 the other therapies. So right from the get-go,
10 you'll have a disproportionate recruitment, and I
11 think it will be very difficult logistically.

12 With regards to the feasibility and regard
13 to the pre- and post-approval cardiovascular
14 outcomes trials, I think that logistically and
15 physically, it's very difficult and likely would
16 preclude approval of this drug.

17 Then finally, with regards to the
18 observational trials with the limitations that we
19 have, I would wonder whether one way to increase
20 the robustness of data accrual, besides these large
21 databases, is a patient-centered approval. I'm
22 actually at a webpage for FDA MyStudies application

1 with regard to patient-related information that
2 would actually potentially increase the robustness
3 of the data collection.

4 DR. LEWIS: Thank you. Dr. Edwards?

5 (No response.)

6 DR. LEWIS: Is she still on the phone?

7 We don't hear you; now we hear you.

8 DR. EDWARDS: As a geriatrician, I have to
9 take into account the aging of America, and it's
10 not trite because we're seeing a very high rate of
11 cardiovascular disease in older adults, and that's
12 exactly the group with osteoporosis, rising as high
13 as 80 percent in the group over the age of 80.

14 So yes, this appearance of this adverse
15 event is worrisome, but there are multi-morbidity,
16 which many of our patients carry, and they can well
17 be extracting [indiscernible] themselves.

18 If you look at the causality and you just
19 follow Bradford Hill's criteria for causality, you
20 see the element of temporal relationship, where,
21 yes, the drug was given before the event, but
22 there's no dose response. There's no biologic

1 feasibility. And that's what I was asking about
2 when I was asking about the basic studies. And the
3 genetic studies show that people with genetic
4 deficits or knockouts don't have this problem of
5 cardiovascular disease.

6 There is no consistency, and we probably
7 have to think of alternative hypothesis. The
8 question, as everyone's been expecting, is how do
9 you design the study? It would have to be
10 postmarketing. A registry might work, but if you
11 look at the map of America and you look at
12 cardiovascular disease in women, it is not even
13 evenly distributed. We have basically the stroke
14 belt as the most coronary disease in the country.
15 So how do you control for all those elements of
16 just the aging?

17 It's not just the hypertensive and
18 diabetics. Aging itself is a risk factor, and that
19 would basically put every woman we have, who's over
20 65, at risk of heart disease. So how do you select
21 the low-risk patient?

22 I think it's very challenging going forward.

1 It's going to be an excellent drug for women who
2 have not been able to tolerate or have complex
3 disease, but being able to exclude the heart
4 disease is going to be as I said because this is so
5 prevalent. And the numbers in the older age
6 segment are just going to continue to grow. So
7 yes; let's add more confusion to this question.

8 DR. LEWIS: Thank you. Dr. Rosen and then
9 Dr. Shaw.

10 DR. ROSEN: So I want to make four points.
11 The first is in response to question 1, we
12 certainly don't have enough data. Two, this is a
13 very efficacious drug. I mean, it's the best thing
14 we've seen in osteoporosis, and that really has to
15 be considered.

16 The third point I want to make is we really
17 don't have enough data at the basic level to really
18 get a good appreciation of what sclerostin is doing
19 or what an anti-sclerostin antibody does to the
20 cardiovascular system. And that's really extremely
21 irrelevant to the whole point of whether we have
22 biologic plausibility or not.

1 I'm a little surprised that the sponsor has
2 not done more at that level. I'm surprised the FDA
3 hasn't gone and looked at some of the patients that
4 have sclerosteosis or Van Buchem's disease, to
5 really characterize lifelong anti-sclerostin
6 production and determine whether or not there is
7 some biological plausibility.

8 There are a number of other SNPs associated
9 with increase in bone density that are also
10 associated with greater cardiovascular risks, so a
11 much more complete coverage of that as indicated.

12 I think that brings us to the last point
13 about alendronate that I wanted to make. I just
14 don't think there's been a signal from all the data
15 we've seen on meta-analysis. Dr. Bauer pointed out
16 the PLOS review of 64 studies in 2015. There are a
17 number of them. That data set has been looked at.
18 Nitrogen-containing bisphosphonate data sets have
19 been looked at. There just does not appear to be a
20 signal for cardiovascular protection.

21 So this one trial is where some of our
22 concerns lie, and I would argue that we need this

1 drug for osteoporosis. I think we need more, both
2 basic work, and I would favor Dr. Bauer's comments
3 that it is possible that we could do a randomized
4 trial with comparative effectiveness of an
5 anti-osteoporosis drug versus romosozumab, and the
6 point of the early effects occurring within the
7 first year may make it less burdensome in terms of
8 doing a long-term study.

9 DR. LEWIS: So you're saying pre-approval.

10 DR. ROSEN: I'm saying post-approval. I
11 said approval with a post-approval comparative
12 effectiveness study.

13 DR. LEWIS: Thank you. Dr. Khosla?

14 DR. KHOSLA: Just to respond to Cliff,
15 Cliff, wasn't Ian Reid's study recently -- did that
16 not show cardiovascular protection with
17 [indiscernible]?

18 DR. ROSEN: It was the secondary outcome
19 that really wasn't -- it wasn't done with multiple
20 comparisons, so it was unclear. I mean, he
21 inserted it, but, yes, it's a secondary outcome.

22 DR. KHOSLA: That was just a follow-up.

1 I'm just coming back to the clinical point
2 that I'm interested in, which is it's going to be
3 almost impossible, in my mind, to definitively
4 answer the cardiovascular issue other than through
5 a huge trial.

6 If you start with the premise that there
7 probably is an effect, for all the reasons that
8 we've talked about, then really as a clinician, the
9 question I have is that if I choose the patients
10 appropriately, is there still an effect?

11 So if you then argue that -- if you label it
12 in terms of the cardiovascular risk and it's only
13 used in people who haven't had a recent MI or
14 stroke, and whatever postmarketing surveillance is
15 done, whether it's observational or registry based,
16 and you don't really see a meaningful signal there,
17 then for clinicians, it's going to I think inform
18 them that used in that way, it is a relatively safe
19 drug that's giving you remarkable skeletal
20 benefits.

21 Yes, in the high-risk cardiovascular
22 patient, we may never know the answer, and we may

1 be withholding the drug from those patients, but
2 then you're benefitting a lot of patients at the
3 same time and not withholding it from them. So I
4 think that's a somewhat different perspective,
5 perhaps a more pragmatic clinical perspective.

6 DR. LEWIS: Thank you.

7 Thank you for all the great discussion
8 comments. It's virtually a consensus, 100 percent,
9 actually, that, no, we don't have adequate data
10 characterizing the cardiovascular safety of the
11 drug. We've had lots of ideas about ways to
12 collect data to further characterize the safety
13 profile cardiovascular-wise.

14 A few people think that this must be done
15 pre-approval. Most people think that post-approval
16 is possible. We've had some suggestions about
17 registries versus a randomized trial with looking
18 at comparative effectiveness.

19 It's been pointed out that the numbers are
20 daunting in terms of thinking about cardiovascular
21 disease as the primary outcome, so most people have
22 looked at other types or talked about other ways

1 that sponsor might approach the question with FDA.

2 Certainly, if these data are acquired
3 post-approval, the black-box warnings do make it
4 challenging to try to recruit an appropriate
5 population because of the tremendous overlap
6 between those who would most benefit from the drug
7 and those at great risk for cardiovascular disease.

8 In a related question, we're going to move
9 to the second question, and that is that Amgen is
10 seeking the indication for treatment of
11 osteoporosis in postmenopausal women at high risk
12 of fracture, defined as a history of osteoporotic
13 fracture, multiple risk factors for fracture, or
14 patients who failed or are intolerant to other
15 available osteoporosis therapies.

16 Discuss whether the benefit-risk profile
17 could be improved by further narrowing the
18 population to patients at low cardiovascular risk,
19 and, if so, how would we define that narrow
20 population?

21 Let's start the discussion with
22 Dr. Dmochowski.

1 DR. DMOCHOWSKI: I'd like to commend
2 Dr. Khosla on his response because this question
3 really is a nuanced, if you will, corollary to the
4 first question. I personally, going back to the
5 first question, would recommend approval of this
6 based upon the efficacy, but then figure out how
7 pragmatically we aim this drug, because we don't
8 really understand that, even to the point of where
9 do we put the box warning in terms of a general
10 selection of patients.

11 I don't think a simple study's going to give
12 us the answer because we don't have enough
13 information on the patients that are fed into the
14 trial. So part of the benefit-risk profile is
15 understanding a much larger cache of patients, if
16 you will, who have been, if you will, categorized
17 with a little bit more of a focus on some of the
18 cardiac risk factors, not just demographics, but
19 for instance, someone mentioned a cardiac scan to
20 do cardiac calcification.

21 Some other things that are cardio -- I'm not
22 a cardiologist, so I can't speak to some other

1 generalistic things that could sort of help us set
2 overall population risks. But this is going to
3 come down to how we best make choices for these
4 individuals who critically need something that
5 appears to have great efficacy.

6 So again, I want to commend Dr. Khosla for
7 his comment because it really, for me, answers this
8 question.

9 DR. LEWIS: Thank you. Dr. Khosla? No?
10 I'm sorry. Dr. Adler?

11 DR. ADLER: Adler. As an endocrinologist, I
12 deal with nuances every day, and I really think
13 that the kind of clinician who is going to use this
14 drug is used to dealing with benefits and risks and
15 trying to tailor therapy to a given patient. I
16 think that clinicians who would be scared of this
17 drug will run the other way and certainly not use
18 this medication.

19 I also want to echo what Dr. Edwards said,
20 and that is that the patient population who is at
21 highest risk for osteoporotic fracture, older
22 folks, age is a major risk factor. Age is also a

1 major risk factor for cardiovascular disease.

2 So it is not going to be surprising that any
3 sort of postmarketing study is going to be
4 relatively enriched, even if we eliminated the
5 1-year post-MI and post-stroke population. So it
6 still will be quite enriched just because of the
7 age of the folks who have fracture and are at high
8 risk, and would therefore be good candidates for
9 this drug.

10 So I think that it ought to be a
11 postmarketing study, and I think the indication is
12 a very reasonable one because it is going to target
13 those people who are at the highest level of
14 potential benefit.

15 DR. LEWIS: Thank you. Dr. Lincoff?

16 DR. LINCOFF: Thank you. I agree with the
17 indication. I want to bring up one side point to
18 that. Getting back on the cardiovascular risk, I
19 think Dr. Sabatine put it well. You have to focus
20 on the group that has the highest underlying risk
21 in that first year. It's a year of therapy, and
22 the risk is during that year because we saw,

1 clearly, if it exists at all, it attenuated by
2 3 years afterward.

3 So what can we do to identify a group of
4 patients that are highest risk in that year? There
5 are all kinds of risk calculators, and they change
6 every couple years when the guideline committees
7 come out. But the bottom line is that having had a
8 recent MI or stroke pretty much identifies the
9 highest-risk groups.

10 In general, therapies that have some risk
11 generally have about the same relative risk.
12 Obviously, there are exceptions, but I don't think
13 we'd expect different risk groups to see different
14 relative risks. So the absolute risk, if we really
15 want to focus away from people at highest risk, I
16 think this is a reasonable approach.

17 It's also an approach that has an endpoint.
18 So you can say I know you've had these fractures,
19 but a year from now, it may be safer to put you on
20 it, at least until we get more data.

21 So I think the rather simple approach,
22 rather than trying to make this unfeasibly

1 complicated, again with practitioners who are used
2 to dealing with risk and benefit with complex
3 drugs, I think is sufficient.

4 I did want to ask, though -- one of the
5 indications here is who failed or are intolerant to
6 other available osteoporosis therapy. Since this
7 therapy was used in the trials followed by an
8 antiresorption drug, and in fact, the one trial
9 that you showed where the bone density declined
10 when an antiresorption drug wasn't given afterward
11 over the course of about a year, almost to
12 baseline, I wonder to limit the risk, or to
13 eliminate a group that may not have much benefit,
14 if we wanted to not use it in people who couldn't
15 get an antiresorption drug afterward. It's just a
16 consideration.

17 DR. LEWIS: Thank you. Dr. Shaw?

18 DR. SHAW: Thank you. So I think this issue
19 of risk-benefit is really important, obviously, in
20 a drug that has been shown to have such great
21 efficacy. There are a couple things to consider
22 here that I think are very important. The first

1 is, going back to what was said earlier, we haven't
2 done a good job of really understanding the
3 risk-benefit profile within a patient. We look
4 separately at risks and separately at benefits.

5 I know there was a concern raised earlier
6 that it's difficult and so subjective to ask a
7 patient what's worse, a stroke or a hip fracture?
8 But actually, for the trials that were done, there
9 was extremely good follow-up, I think 80 percent up
10 to 3 years.

11 Certainly, looking at MACE and hip fractures
12 in the events that happened, if you took 2 random
13 patients on each arm and asked a doctor to say who
14 did better or worse, you might look at one patient
15 who had a hip fracture early on and another patient
16 who had a mild MI that recovered.

17 So I think those kinds of analyses, there's
18 been a ton of work in the last couple years with
19 the data you have that could actually add more
20 understanding of, perhaps, even greater risk
21 risk-benefit balance than you realize.

22 I would be careful going forward, being too

1 myopic about cardiovascular safety only in that
2 first year because we know that hip fractures are
3 followed by high levels of mortality and other
4 cardiovascular events, and depression that leads to
5 further morbidity. I would want to see these
6 studies, say, if they're done either pre- or post-
7 approval, that would come up with composite
8 endpoints that put risk-benefit together, so we
9 have some understanding in the short term and in
10 the long term what's happening to these patients
11 overall.

12 I think if we start with the narrow
13 population, where we're really comfortable with
14 that risk-benefit balance, that could help
15 understand the trade-offs with other patient
16 populations, as we see are the cardiovascular
17 events in the frailer patients that are also
18 getting fractures, and this might help move forward
19 with other populations.

20 DR. LEWIS: Thank you. Ms. Portis?

21 MS. COMPAGNI-PORTIS: With this question
22 about could we improve by further narrowing the

1 indicated population, I go back to I don't think we
2 know who was at risk. Again, to Dr. Shaw's point,
3 it's like we were talking about risk, but we don't
4 really know, with the data we have who's at risk.
5 So I don't know how we could even meaningfully
6 limit the population.

7 As a patient with osteoporosis, with a
8 history of breast cancer, and a family history
9 that's serious there, I don't know how I could have
10 a meaningful conversation with my physician without
11 having more data about what is the risk for an
12 individual, so that I could get fully informed
13 consent, because, yes, I think those conversations
14 are essential, and good doctors have them with
15 their patients all the time. But I think we would
16 be kind of swinging in the dark without having more
17 information on this.

18 DR. LEWIS: Thank you. Dr. Burman?

19 DR. BURMAN: Thank you. I just wanted to
20 focus on the term that was brought up earlier,
21 "intolerant." As was mentioned, if you're
22 intolerant to bisphosphonate, then you're not going

1 to be able to take it, quote/unquote, "when you
2 finish the drug after one year." But also even the
3 term itself "intolerant" is too vague.

4 This came up with other committee meetings
5 with cholesterol drugs, et cetera, that it should
6 be better defined to really make it more likely
7 that the intolerance is really related to the
8 medication itself.

9 DR. LEWIS: Thank you. Dr. Wang?

10 DR. WANG: Yes. I think the point that was
11 raised earlier is an important one, the difference
12 of relative risk and absolute risk. There's
13 nothing in the data that suggests that the
14 relative -- actually, we'll call it the relative
15 harm, or the potential relative harm for this drug
16 varies by subgroup, with the caveat that the
17 subgroups are even further away from firm grounding
18 in the data. But for most drugs, there's not
19 effect modification, so if there's harm, it tends
20 to be relatively consistent between groups.

21 So I would agree with Dr. Lincoff's comment
22 that the risk profile is going to be largely driven

1 by absolute risk. And although we don't have a lot
2 of data from the romo trials, we have an enormous
3 body of data from the cardiovascular literature.

4 So I think that this discussion of
5 risk-benefit can at least start with the absolute
6 risk of cardiovascular disease, which is a
7 discussion that physicians can have with their
8 patients, even though these data may not exist in
9 the romo trials.

10 Although I agree there's a lot of
11 uncertainty, I just don't want people coming way
12 from this feeling that we're totally in the dark.
13 We can have a semi-informed conversation about
14 baseline cardiovascular risk with our patients, and
15 people at the extreme of that, extremely low or
16 extremely high risk, are likely because the
17 relative risk estimates probably aren't that
18 variable. In those people, you can probably be
19 within the ballpark of understanding what the
20 impact of the drug if there is a real harm
21 cardiovascularly.

22 The second point that I would make is really

1 a question, which is if we're of the belief that
2 narrowing the population that we target this drug
3 to, to people not at very high risk -- and I agree
4 with Dr. Lincoff, the easiest way is to say people
5 without prior MI or stroke -- does the FDA consider
6 that the best mechanism for that is a black box or
7 actually putting it in the top line indication?

8 I raise that because my understanding is,
9 for it to actually end up in the indication
10 suggests that you've done a prospective study
11 looking at that population, which obviously this
12 came up afterwards.

13 That's more of a question than a comment.
14 In other words, there seems to be different
15 mechanisms to try to get to the population you
16 want, and I'm not certain in my mind whether that's
17 by changing the indication or putting it into a
18 warning.

19 DR. SUAREZ-ALMAZOR: Can I make a comment?

20 DR. LEWIS: Sure.

21 DR. SUAREZ-ALMAZOR: With respect to what
22 you said, I think there is effect modification,

1 though, because when you look at the way the FDA
2 analyzed the data by stratifying whether you had or
3 did not have a cardiovascular 9, the hazard ratio
4 was different, so the effect of the drug is
5 different, according to the risk factor. Well, I
6 don't know. 9?

7 DR. WANG: I imagine the confidence
8 intervals are quite wide. I don't recall there
9 being anything convincing.

10 DR. SUAREZ-ALMAZOR: Well, I don't know.
11 The FDA can say whether you think there is an
12 effect modification or not. Slide 9 on the
13 May [ph] subgroup analysis, month 12.

14 MS. BHATT: Which presentation?

15 DR. SUAREZ-ALMAZOR: Sorry.

16 DR. KEHOE: I think it's my presentation.

17 DR. SUAREZ-ALMAZOR: Dr. Kehoe.

18 DR. KEHOE: Was it my presentation?

19 DR. SUAREZ-ALMAZOR: Yes, number 9.

20 DR. KEHOE: Slide 9 of my presentation.

21 As far as where we would try to narrow the
22 population further than the indication, the

1 indication that the company is seeking is already
2 an indication in other osteoporosis therapy. So it
3 is recognized by the prescribing community.

4 The options for narrowing it further could
5 be the boxed warning. It could also be as a
6 contraindication to specifically state that
7 patients with whatever criteria should not receive
8 the drug.

9 DR. WANG: Just to follow up on that, my
10 understanding from what the FDA has advised is a
11 contraindication means you've established harm or
12 biological mechanism. In other words, I recognize
13 saying it's a contraindicated population is one way
14 to do it, but I don't know that we've achieved that
15 level of evidence here.

16 DR. KEHOE: I think that's very true, and,
17 of course, if we are looking at a postmarketing
18 study, the question then becomes what do you do if
19 it's positive? So if you start with something that
20 is a boxed warning, then at least you have the
21 option that after it has been shown to be a real
22 concern, that you can then move to a

1 contraindication or other things like that.

2 So probably you're right that it's not
3 definitive at this point, so perhaps a
4 contraindication is not the best place.

5 DR. JOFFE: This is Hylton Joffe. I would
6 just say that, for contraindications, we are not
7 supposed to put in theoretical concerns, and a
8 contraindication is defined as a situation when the
9 risks always outweigh the benefits and you should
10 not use the drug in that situation.

11 With regard to the subgroup analyses, I
12 agree with what's been expressed by the company.
13 The event rates are very low when you start slicing
14 and dicing the data. So for example, on slide 9,
15 you're talking about 3 events in the
16 no cardiovascular risk factor at baseline in
17 study 142. You can't really just say anything
18 about that.

19 DR. LEWIS: I'm going to bring us back to
20 the discussion points at hand. Dr. Orza and then
21 Dr. Weber.

22 DR. ORZA: I wanted to first follow up on

1 something that Dr. Shaw said about what we could
2 learn both from the data that we already have and
3 the data that we're talking about collecting
4 through some additional study. It would be really
5 important to have endpoints about quality of life,
6 and functional status, and pain, and all those
7 things that people would want to try to factor in
8 to this kind of a trade-off decision.

9 Then my other things are really questions.
10 One approach is to try to really narrow to the
11 people who would benefit the most and are at the
12 least risk to try to improve the ratio. On the
13 side of trying to hone in on the people who would
14 really benefit the most, I had a question about the
15 middle part of the indication statement for the
16 clinicians in the room.

17 History of fracture seems like they're high
18 risk and failed or intolerant seems like they're in
19 great need. But I wondered about the multiple risk
20 factors for fracture, not having already had one,
21 simply having a clinical definition of osteoporosis
22 that's just about bone density, if that belongs in

1 the indication statement. That was one question
2 for the clinicians in the room.

3 The other question was for FDA. We've been
4 talking about the kinds of practitioners who would
5 be using this and maybe a registry, which under
6 normal circumstances, would be voluntary. I
7 wondered, beyond a black box, whether there are
8 elements of a REMS that we should be thinking about
9 that could actually be a helpful approach to
10 channeling this in the way that we want it
11 channeled and also being able to get more data if
12 it's out there on the market. And I just wondered
13 why that wasn't on the table as a possibility.

14 DR. KEHOE: At this point in time,
15 certainly, REMS would be considered if there was a
16 box, so we could potentially. But the question
17 is -- and some of my DRISK colleagues might want to
18 address this more than I might be able to. The
19 question would be, what could we really do in that
20 situation?

21 DR. ORZA: We've had other examples, where
22 it was a really important good drug that met a

1 serious need, but it had a big downside, so we
2 constructed a REMS around it to try to manage that
3 when it's out there in the world.

4 DR. KEHOE: I'm going to let
5 Dr. Jamie [indiscernible] talk about REMS, but what
6 I would say as far as voluntary registries; we've
7 tried this several times with osteoporosis drugs,
8 and it has not gone well in trying to get any kind
9 of data that is useful.

10 So I think it would have to be something
11 along the mandatory lines, and I'm not sure that
12 data allow us to be there yet.

13 DR. WILKINS: Hi. Jamie Wilkins, Office of
14 Surveillance and Epidemiology, FDA. I would ask
15 the committee what types of elements that you would
16 see for a REMS to mitigate this risk for this
17 particular product in the context of a boxed
18 warning and contraindication.

19 DR. LEWIS: Dr. Gerhard?

20 DR. GERHARD: Just briefly, I think we don't
21 know whether there is a risk, so I think it's hard
22 to talk about what we can do to mitigate the risk

1 that we don't know whether it is true.

2 DR. LEWIS: Dr. Khosla, then Dr. Weber.

3 DR. KHOSLA: I just wanted to respond to
4 your question about the multiple risk factors for
5 fractures. There are in fact ways in which using
6 risk factors for fracture, you can come up with,
7 through FRAX and other calculators, 10-year risks
8 of fracture that would be equivalent to somebody
9 who's already had an osteoporotic fracture.

10 In fact, in the UK, treatment thresholds are
11 based on that, so people who don't have a fracture
12 but have enough risk factors that they have a
13 future risk of fracture equivalent to somebody
14 who's had a fracture are then recommended for
15 treatment. So that's very much part of clinical
16 practice.

17 DR. ORZA: So is there a way to make that
18 phrase more targeted towards really high-risk
19 people or is it adequate as is?

20 DR. LEWIS: You mean in terms of the
21 indication for the drug?

22 DR. ORZA: In terms of the indication, or is

1 it adequate as is, if we wanted to narrow it to the
2 people at highest risk for a hip fracture, who
3 would benefit the most and be willing to
4 potentially tolerate the biggest downside?

5 DR. LEWIS: I think, with that, it's
6 possible, but certainly, I think the biggest, most
7 controversial part that we're worried about is the
8 cardiovascular risk part because both FDA and
9 sponsor have pretty well determined that there's a
10 benefit in the patients who have already been
11 studied. If I could ask the committee to really
12 try to focus on the cardiovascular piece.

13 Dr. Weber?

14 DR. WEBER: Tom Weber. Can I focus back on
15 one other thing for a second?

16 DR. LEWIS: Sure.

17 DR. WEBER: I think that this is a question
18 for the FDA for Theresa and Hylton. The language;
19 we look at risk factors in history of fracture, but
20 I've always been a little bit struck and puzzled by
21 intolerant, because in my clinic, if a patient's
22 intolerant to all available therapies but has a

1 reasonably low or not very high risk of fracture,
2 that's a decision point where you might not offer
3 them a treatment that's going to offer more risk
4 than benefit.

5 So is this language -- I know it's
6 consistent with therapies, but is there any way to
7 alter this, or is this what we're looking at in
8 terms of our choices?

9 DR. KEHOE: I think we could consider it. I
10 think the problem is when you take a condition and
11 you have three or four different indication
12 statements, it's confusion to the prescriber. So
13 we could consider it, certainly, but I'm not sure
14 it's a path that would be beneficial to go down.

15 DR. LEWIS: I don't know. If I could just
16 jump in, it seems like, in clinical practice, we do
17 encounter all the time somebody saying, "I didn't
18 tolerate that." Well, what do you mean? "I took
19 it once. I had indigestion." Okay. Let's talk
20 about whether we might try it again, or how did
21 that happen, or further probe that.

22 So sure, intolerant is very vague, but it's

1 also a term that I think clinicians can figure out
2 how to navigate beyond what's actually in the
3 label.

4 I'm sorry. Dr. Bauer?

5 DR. BAUER: Yes. I've never liked this
6 verbiage for this indication because it's so
7 nonspecific, but I guess as long as it does what
8 it's supposed to do, it doesn't really matter,
9 which is, it's not supposed to be widely prescribed
10 to people that are at low risk. So it basically
11 changes prescriber behavior so that it makes them
12 think twice before they prescribe some other agent,
13 I think I'm okay with it.

14 But I agree. Multiple risk factors; well,
15 who doesn't have multiple risk factors? Failure.
16 How do you define a failure to other treatments?
17 Well, that's almost impossible in our field because
18 we don't know that they wouldn't have had the
19 fracture or more fractures had they not been given
20 an agent.

21 So it's just really a difficult thing to do,
22 and I share your pain, but I think it's not great,

1 but it probably serves the purpose that it's
2 supposed to do.

3 DR. LEWIS: Thank you. I think at this
4 point, we've had a good robust discussion around
5 cardiovascular risk factor, but not a conclusive
6 discussion. Yes?

7 DR. JOFFE: This is Hylton Joffe. I have a
8 quick question. I've heard a little bit of
9 language about avoiding patients who have had a
10 recent heart attack or stroke. I was wondering if
11 we could get a little more granular than that. Is
12 there a certain time period we're thinking about
13 within which that stroke or heart attack happened?

14 Again, we're trying to operationalize this
15 as much as possible for prescribers.

16 DR. LEWIS: Dr. Lincoff, then
17 Dr. Braunstein.

18 DR. LINCOFF: I think most of the
19 cardiovascular literature is within the first year,
20 but obviously that risk, the instantaneous risk,
21 falls over that first year. So to some extent, I'd
22 like the idea of the boxed warning because it's a

1 warning, not a contraindication. It allows some
2 flexibility.

3 I think a patient who is having multiple
4 osteoporotic fractures and is very high-risk there,
5 who's at month 6, you have a discussion. You make
6 the decision together that you still may be at risk
7 for cardiovascular event, but you're really having
8 a lot of issues with your osteoporosis.

9 So I would say within the prior year would
10 be the period, but as a box warning, my
11 understanding is that that allows judgment and
12 flexibility, which I think would be helpful.

13 DR. LEWIS: Dr. Braunstein, then
14 Dr. Gerhard?

15 DR. BRAUNSTEIN: I agree. One year from
16 what the data shows because it falls off, the risk
17 falls off after a year. But also, if an
18 observational study shows no signal down the road,
19 and those patients during the first year after an
20 MI or stroke have been channeled out of that group,
21 that's fine. I think if the sponsors want to get
22 rid of the black-box warning, then they do the

1 randomized study to show that there is no
2 cardiovascular risk.

3 DR. LEWIS: Dr. Gerhard?

4 DR. GERHARD: I think it really depends on
5 what population we're talking about. In those
6 patients that get the drug, we can of course
7 maximize the benefit-risk profile by taking out any
8 people with any type of cardiovascular risk factor.
9 The fewer cardiovascular risk factors we allow, the
10 bigger the benefit-risk fracture will be in the
11 group that gets the treatment. The problem is that
12 we then withhold the drug from a lot of people that
13 would receive a benefit from the drug.

14 That brings us back to the point that
15 without knowing whether there is a risk and how big
16 it is, trying to find the right cut point of who
17 should get the drug and what level of
18 cardiovascular risk is the drug supposed to be
19 given versus not is a moot point.

20 DR. LEWIS: Thank you. Dr. Suarez-Almazor
21 and then Dr. Nahum.

22 DR. SUAREZ-ALMAZOR: Yes. I'm a little

1 confused about the last part of this discussion.
2 Are we talking about the actual language that would
3 go in the boxed warning, whether it's going to be
4 just reflecting that there's an increased risk for
5 MI and stroke versus saying that this would be
6 increased in patients who have a prior history
7 within the past year?

8 I'm a little confused, whether this is just
9 during the first year, of what the actual wording
10 on the warning would be and whether we are
11 suggesting a modification on that. I don't know
12 that that was shown by the sponsor, what the actual
13 wording would be or not. Do you have that?

14 DR. LEWIS: We haven't been shown an actual
15 warning. We're trying to talk about a population,
16 what population would be at low risk and how would
17 you define them, low risk for cardiovascular
18 disease and how would you define them. I don't
19 think we're talking about an actual labeling here,
20 are we?

21 DR. ORZA: C-17 is where the sponsor showed
22 what they proposed.

1 DR. LEWIS: Yes, yes. That's the sponsor's
2 proposal, but we're not here to vote on that.

3 DR. JOFFE: This is Hylton Joffe. The FDA
4 and the sponsor, if the decision is to approve the
5 drug, will have a lot of discussions on what the
6 actual wording should be. We're trying to get the
7 concepts here in as clear a way as possible on
8 something that could be operationalized for
9 healthcare providers, because if you just tell them
10 low cardiovascular risk, it's very fuzzy, kind of
11 like some of the comments that are being made about
12 some of the other wording in the indication.

13 So anything that's practical and that could
14 be widely understood by clinicians would be very
15 helpful.

16 DR. SUAREZ-ALMAZOR: But the comments that
17 were made then were just made with respect to
18 narrowing the population or also with respect to
19 the labeling? I'm not sure --

20 DR. LEWIS: They're interested in narrowing
21 the population. People have talked about a lot of
22 things.

1 DR. JOFFE: Right. We'll take this back,
2 and then if the drug is going to get approved, have
3 further discussions with the company on what the
4 actual exact wording would say in the label, where
5 it would go in the label, et cetera.

6 DR. LEWIS: Dr. Nahum?

7 DR. NAHUM: Thank you. Dr. Nahum. I'd like
8 to agree with what Dr. Gerhard said previously, and
9 I'm going to go back to another comment that I made
10 previously.

11 I am not clear, and perhaps the sponsor has
12 data about this or maybe the FDA has data about
13 this, as to what the level of overlap is between
14 the clause in the indication, defined by a history
15 of osteoporotic fracture, multiple risk factors for
16 fractures, or patients who have failed or are
17 intolerant to another available osteoporosis
18 therapy on the one hand, and the population that's
19 at low cardiovascular risk at the other end.

20 In other words, if there's no big
21 intersection of these two ideas, then there's going
22 to be not very many people who will be eligible to

1 receive this drug. So a lot goes into how you
2 define these terms. Okay? I think the indication
3 is pretty well defined, and the idea about the
4 indicated populations, patients who are at low
5 cardiovascular risk, that's a little bit more
6 nebulous.

7 So unless that's better defined and unless
8 there is data to support the idea that these are
9 truly populations that can be distinguished that
10 are not completely overlapping, then we're
11 effectively putting labeling on a drug, saying
12 nobody can get it. Anybody who needs it is
13 ineligible because they have high cardiovascular
14 risk or higher than we'd like. And anybody who's
15 at low cardiovascular risk may not have the
16 osteoporotic and fracture criteria to receive it.

17 So I think I'd like to see some data around
18 this to decide what the criteria should be for
19 narrowing the populations before any kind of
20 wording should be chosen for this.

21 DR. LEWIS: Dr. Adler?

22 DR. ADLER: Yes. I just want to speak to

1 that, and I think what we have heard from
2 Dr. Lincoff I think may help us here. And that is
3 if we eliminate those people at the highest
4 cardiovascular risk, because they've had an MI or
5 stroke in the last year, that means there a lot of
6 people that are going to be from low to moderate
7 and even some relatively high cardiovascular risk.

8 So I don't think the indication should be
9 those of low cardiovascular risk because I don't
10 think we'll find those. I think, rather, we should
11 eliminate from the use of this drug those who we
12 have good data, that they're at the very highest
13 risk, and we should discourage use in those people.

14 DR. LEWIS: Since we all started with a
15 place where we understand that the risk isn't
16 adequately described, it's not surprising that it's
17 been difficult for us to figure out who would be
18 the low risk population that could be appropriately
19 characterized here.

20 However, the closest we've come to a
21 consensus is that those who we know have a very
22 high risk of heart attack. Those who just had a

1 heart attack or cardiovascular disease event within
2 the last year would be at the highest risk for
3 having another event independent of whether or not
4 they take this drug. That would be a population
5 that would seem to be a high-risk population or
6 probably those who we would discourage from taking
7 the drug.

8 At this point, I believe we're ready to look
9 at the final question, which is the voting
10 question. Is the overall benefit-risk profile of
11 romosozumab acceptable to support approval? Three
12 choices here; yes for Amgen's proposed indication,
13 treatment of osteoporosis in postmenopausal women
14 at high risk for fracture defined as a history of
15 fracture, multiple risk factors for fracture or
16 patients who have failed or are intolerant to other
17 available osteoporosis therapy; B, yes, but for a
18 different indication; C, no.

19 We're going to vote first, and then you'll
20 be able to provide a rationale for vote. And if
21 you vote B, we will ask you to describe the
22 population in whom the benefit outweighs the risk.

1 Clarification on the wording?

2 DR. BAUER: Need a clarification. So how
3 does the black box fit into this A-or-B?

4 DR. JOFFE: That was my question, too.

5 DR. LEWIS: I want this question answered
6 first, yes.

7 DR. JOFFE: I'm wondering if we should think
8 about this from a patient population perspective.
9 Do you think it's A for Amgen's patient population
10 that they're proposing; B, yes, but for a different
11 population; or C, no.

12 Would that make it clearer, as opposed to
13 getting into the details of where specifically it
14 goes in the label? Amgen has already agreed to do
15 a boxed warning, so it's more who are the patients
16 who should be getting this drug?

17 DR. LINCOFF: So if we agree, but also want
18 the boxed warning, can we vote A?

19 DR. JOFFE: Yes, because Amgen is proposing
20 a box, and you've heard what Amgen is proposing.
21 They're proposing a box. First of all, they're
22 proposing this specific indication, and then for

1 the box, they're proposing excluding patients who
2 had a recent MI or stroke.

3 So if that paradigm sounds correct to you,
4 you would vote for A. If you think it should be
5 different to that, vote for B. And if you think
6 there's no one who should be getting this drug,
7 vote for C, and then provide rationale.

8 Is that clear?

9 DR. LEWIS: Dr. Weber?

10 DR. WEBER: This is Tom Weber. This follows
11 up on my point about the indications and the
12 language for the indication. It almost looks like
13 it's opening -- in regards to what's described,
14 especially in terms of patients intolerant of
15 therapy. So does that incorporate B in terms of
16 labeling in postmenopausal women or am I thinking
17 about this wrong?

18 DR. KEHOE: If you think there should be a
19 different indication than what's stated in A, that
20 it should be worded differently, then you would
21 vote B.

22 DR. BAUER: Can I ask a quick question? So

1 how are we supposed to incorporate our, in some
2 cases, very strong feelings about the need for
3 postmarketing studies into this vote?

4 DR. KEHOE: If you believe the postmarketing
5 studies should be done pre-approval, you would vote
6 no. But other than that, if you believe it should
7 be done post-approval, then we're taking what
8 everybody said in one, but that would be a vote for
9 either A or B.

10 DR. JOFFE: Is it clear? We want to make
11 sure the question's as clear as possible before
12 folks vote.

13 (Laughter.)

14 DR. LEWIS: Question is clear? Everybody's
15 ready?

16 (No response.)

17 DR. LEWIS: If there is no further
18 discussion on the question, we will now begin the
19 voting process. We will be using an electronic
20 voting system for this meeting. Please press the
21 button on your microphone that corresponds to your
22 vote. You'll have approximately 20 seconds to

1 vote. Please press the button firmly. After you
2 have made your selection, the light may continue to
3 flash.

4 If you are unsure of your vote or you wish
5 to change your vote, please press the corresponding
6 button before the vote is closed. After everyone
7 has completed their vote, the vote will be locked
8 in. The vote will then be displayed on the screen
9 and will be read from the screen into the record.

10 Is everyone ready? A is 1, B is 2, and C is
11 3. We're all clear? A, B, C, 1, 2, 3.

12 DR. JOFFE: I think what folks are saying
13 is, at least on mine, A is under attend, B is under
14 yes, and C is under no. So just to confirm it,
15 because we have had issues sometimes with multiple
16 choice before, and the advisory committee staff
17 confirm, if you're voting A, you push the button
18 that has "attend" written above it or A below it; B
19 would be the yes, B, button; and then C would be
20 the no, C.

21 MS. BHATT: That's correct. Yes, correct.

22 DR. JOFFE: Attend is A, yes is B, no is C.

1 You all are too far removed from standardized
2 testing, I guess.

3 DR. LEWIS: When you provide the rationale,
4 if you think you made a mistake, we'll get that,
5 too.

6 (Voting.)

7 MS. BHATT: The voting results; A is 15, B
8 is 3, and C is 1.

9 DR. LEWIS: We're going to start with
10 Dr. Kushner because I think he has to make a plane.

11 DR. KUSHNER: Thank you. I voted yes. I
12 think there's a tremendous need for this
13 medication. I think there's an amazing amount of
14 morbidity and mortality associated with the
15 disease, and this can be helpful to many, many
16 people.

17 I think it's proven its efficacy, and the
18 safety issue is still unknown. But I would vote
19 for approval with a black-box warning and then a
20 postmarket study that would include possibly A, a
21 prespecified and randomized registry type trial to
22 identify patients who might or might not be at

1 increased risk. I'm not sure there really is a
2 safety signal.

3 Thank you. I did not want to change the
4 indication. I was confused with your marking on
5 your buttons here. On my buttons, it said A was
6 yes, so I wanted to vote A.

7 DR. LEWIS: Does that mean we have to do
8 something again before he leaves? We're all set?

9 DR. KUSHNER: Just move me up to the A box.
10 (Laughter.)

11 DR. KUSHNER: Thank you.

12 DR. LEWIS: Very good.

13 We can go around the room, then.

14 Dr. Suarez-Almazor?

15 DR. SUAREZ-ALMAZOR: Yes, Maria
16 Suarez-Almazor. I voted yes. I think osteoporotic
17 fractures, particularly hip fractures, have even
18 more deleterious effects sometimes than what
19 cardiovascular events might have.

20 This is a new drug that has a dual
21 mechanism, both on bone formation and bone
22 resorption, and as such is the only one with the

1 mechanism that would be offered in the market, and
2 it has shown clinically that it's very efficacious.

3 I think that the box warning as proposed and
4 the postmarketing study, with the data that we
5 have, which I recognize is poor and it's
6 inconsistent, is sufficient at this time to proceed
7 with the marketing of the drug in my view.

8 DR. LEWIS: Thank you. Dr. Lincoff?

9 DR. LINCOFF: Michael Lincoff. I voted yes,
10 A, and I've had the opportunity to express my
11 thoughts, and I won't belabor them by repeating
12 them.

13 DR. LEWIS: Dr. Blaha?

14 DR. BLAHA: Yes, Mike Blaha. I voted A. I
15 found, actually, the sponsor's proposal very, very
16 reasonable in this case, given the morbidity and
17 mortality associated with fracture, how significant
18 of a clinical outcome that is, given the
19 uncertainty about the cardiovascular disease risk.

20 I think the proposal by the sponsor for a
21 black box shows some attentiveness to the potential
22 of cardiovascular risk and openness to doing some

1 sort of a postmarketing study, which I know is
2 going to be an ongoing discussion. I think that's
3 great. Experts can work that out. I find it very
4 reasonable to approve under those circumstances.

5 DR. LEWIS: Thank you. Dr. Wang?

6 DR. WANG: I also voted A. I made my
7 feelings clear, but I'll read some of them into the
8 documentation. My vote is based on the strong and
9 clear evidence of efficacy of this drug. It
10 certainly doesn't disregard the possibility that
11 there's a cardiovascular risk signal. It's an
12 important consideration that I think warrants
13 further investigation.

14 That being said, as others have articulated,
15 even if the modest cardiovascular signal is real, I
16 think you need to weigh the signal against the
17 clear benefits of the therapy on osteoporosis and
18 clinical fractures. And at the individual patient
19 level, that balance may well vary.

20 So to that end, I also agree with the
21 recommendation that the sponsor has moved forward
22 with, which is to include a black-box warning.

1 With regard to the need for more data, I
2 agree that a cardiovascular outcomes trial is the
3 gold standard. I've also mentioned some of my
4 concerns about the feasibility of doing this, so
5 I'll leave that question aside. I think more
6 studies are warranted, but I think it's reasonable
7 to have those studies take place in the
8 postmarketing/post-approval setting.

9 DR. LEWIS: Let's get Dr. Wang from the
10 phone. I'm sorry, Dr. Edwards from the phone.

11 DR. EDWARDS: I voted A for the reasons that
12 most of the other investigators are citing. It's
13 an effective drug, and the older adults are in
14 particular need of such drugs to keep them
15 functionally independent. We'll see about the
16 cardiovascular events, whether they're real or
17 they're just associated with aging. For many of my
18 patients, that is very true.

19 In addition, there are patient groups that
20 we haven't talked about here that we're just now
21 starting to find out the risks and outcomes of
22 fractures, for which I think a drug such as this

1 will be very helpful going forward.

2 DR. LEWIS: Thank you. Dr. Shaw?

3 DR. SHAW: Hi. So I voted yes because of
4 that clear indication of efficacy in a very
5 compelling population of who needs it in contrast
6 to a weak to confusing signal for the safety.

7 I really want to emphasize that a large part
8 of our population could get this drug, so I would
9 really like to say that my yes is relying on a
10 high-quality postmarketing study, on maybe not just
11 the risks in a cardiovascular-outcome-only trial in
12 1 year, but the risk-benefit, the trade-off that we
13 consider the research that's out there with a lot
14 of recent methods on even a primary outcome that
15 might be the risk-benefit composite, and that that
16 should be part of the postmarketing because there
17 are benefits as well as risks in terms of
18 mortality.

19 DR. LEWIS: Thank you. I also voted yes.
20 The only thing I will add to what's already been
21 said is that I think a postmarketing study of high
22 quality in the United States is really important to

1 do because, although the data are very clear that
2 you've presented, we really don't know what this is
3 going to look like in the United States, except
4 that I have confidence that it will be effective,
5 which is the main reason I'm voting yes. I do
6 think that it's important to study a U.S.
7 population.

8 DR. BAUER: Doug Bauer. I also voted yes
9 for all the reasons that have been so well
10 articulated before me. I'll just reiterate that my
11 vote was sort of contingent upon that follow-up
12 study and also the hope that the black box can
13 eventually be removed if it turns out that this in
14 fact is a spurious association, which it could be.

15 DR. DMOCHOWSKI: Roger Dmochowski. I voted
16 yes. I don't think I have anything to add. It's
17 just really contingent on a good postmarketing
18 study, which I think will be a very creative study
19 for sure.

20 MS. COMPAGNI-PORTIS: Natalie Compagni-
21 Portis. I voted no almost for the same reasons
22 people voted yes. I think there's a great need and

1 I think there's real potential with this drug, and
2 I think we might find out with doing the research
3 that we could very widely and safely prescribe
4 this. But I think it behooves us to clarify the
5 safety issues prior.

6 DR. LEWIS: Thank you. Dr. Orza?

7 DR. ORZA: Michele Orza. I found myself
8 between a rock and a hard place and took the
9 coward's way out and voted B. I'm assuming that
10 even if the cardiovascular endpoints -- the signal
11 turns out to be real, that perhaps not on a
12 population basis, but on an individual basis, that
13 the risk-benefit trade-off could be worth it.

14 I voted -- I was going to vote no because I
15 was leaning toward a pre-approval study because I
16 think we have to take the need for additional
17 information very seriously and make sure we get it.

18 I was trending toward yes because of the
19 need and the benefit that could come from this.
20 But I think there really needs to be attention paid
21 to -- I really would like to see a REMS considered,
22 and I really would like to see, in the process of

1 getting more information about this drug, help for
2 patients and clinicians to really make this risk-
3 benefit trade-off together.

4 So I think that's going to take not only
5 what FDA puts in the label, but what the clinical
6 societies come up with in their guidelines, what
7 the sponsor is willing to come up with in terms of
8 patient support materials, what the patient groups
9 are able to come up with.

10 I think it's going to take an army of people
11 to really help people make this risk-benefit
12 trade-off, because I think, at the individual
13 basis, it's going to be a tough call.

14 DR. ADLER: Robert Adler. I voted yes. And
15 Dr. Bauer expressed my thoughts better than I
16 could.

17 DR. LEWIS: Dr. Braunstein?

18 DR. BRAUNSTEIN: Glenn Braunstein. I voted
19 yes. I think the efficacy of this drug was superb.
20 If I had to bet, I would bet that the
21 cardiovascular issue in 142 is going to turn out to
22 be spurious, but we have to live with the data that

1 we have now. And therefore, I hope the sponsors
2 will do a study that will get rid of the black box
3 that they've agreed to put in. Thank you.

4 DR. LEWIS: Thanks. Dr. Khosla?

5 DR. KHOSLA: I voted yes, and I agree with
6 the comments that have been made. I think a very
7 important drug, plus/minus in terms of the risk,
8 and I think we've discussed mitigating that risk

9 DR. LEWIS: Thanks. Dr. Burman?

10 DR. BURMAN: Thank you. I voted yes for
11 many of the same reasons. I want to congratulate
12 the FDA and the sponsor for excellent
13 presentations. The drug does have important
14 benefits. I think a cardiovascular outcomes trial
15 should be done postmarketing.

16 I just raise the issue quickly of the
17 black-box warning for MI and stroke, but as an
18 endocrinologist, it may be a little more
19 complicated than that; for example, someone with
20 familial hypercholesterolemia who has a cholesterol
21 that's extremely high, et cetera. So there are
22 other subtleties to think about. Thank you.

1 DR. LEWIS: Dr. Rosen?

2 DR. ROSEN: I voted yes for all the reasons
3 that people talked about, the efficaciousness of
4 the drug. I would applaud the sponsors for their
5 presentation and also for their presentation of a
6 potential black box, which I think is probably
7 indicated. And I would argue for more both
8 preclinical data and a postmarketing clinical
9 trial, possibly a comparative effectiveness trial.

10 It's very reminiscent. I haven't been on
11 this committee for 10 years, but this is very
12 reminiscent of the old diabetes days, where we had
13 a 30 percent greater risk, and sponsors had to do
14 the randomized trial to establish whether or not it
15 was real or not, and I think this is where we are,
16 too.

17 DR. LEWIS: Thank you. Dr. Weber?

18 DR. WEBER: This is Tom Weber. As we've
19 heard today, osteoporosis is a significant health
20 problem, health crisis, and it's both
21 underdiagnosed and undertreated. In addition, we
22 have limited options for patients who are severely

1 affected based on fracture burden or high risk of
2 fracture, however, we need to balance the risk and
3 benefit; as we are charged as physicians, do no
4 harm, or actually it should be do as little harm as
5 humanly possible.

6 There's unclear cardiovascular risk with
7 romosozumab, but given some certainty, restriction
8 of labeling to patients who have had a heart
9 attack, not to give it to them who have had a heart
10 attack, MI, or stroke within a year seems
11 reasonable and defined by a black-box warning.

12 Understanding we could be restricting
13 treatment with the drug from people who need it, we
14 do have other FDA-approved options for treatment of
15 osteoporosis who are not leaving them untreated. I
16 agree with plans for a postmarketing observational
17 study and would favor a REMS program to obtain as
18 robust data as possible to address that.

19 Regarding my vote of B, I would vote to
20 remove intolerance of therapy because I don't think
21 that necessarily confers a high risk of fracture.
22 Having said that, for the record, since I'm in the

1 distinct minority here, if that's not possible, I
2 would be happy with a vote of A.

3 DR. LEWIS: Thank you. Dr. Gerhard?

4 DR. GERHARD: Tobias Gerhard. I voted A. I
5 think the colleagues on the panel have provided
6 ample justification of what the need for the drug
7 is and what the benefit of the drug is, so I want
8 to focus on the postmarketing studies required to
9 kind of assess or quantify the cardiovascular risk,
10 potential cardiovascular risk, and would just urge
11 FDA to insist on a postmarketing approach that
12 includes randomization because I am very confident
13 that you will not get the correct result.

14 You will find the drugs with an
15 observational study -- purely observational study,
16 you'll find the drug safety no matter what just
17 because of the channeling, and that's predictable,
18 and we're not doing public health any good if we
19 follow that path.

20 I think large simple trials might be an
21 approach here. I fully acknowledge that large
22 simple trials are not simple, but I think here, it

1 is a feasible option and it's a necessary option.

2 Just one very quick last statement; that
3 set-up of a large simple safety trial would
4 actually also facilitate potentially the evaluation
5 of some of the benefits, particularly hip
6 fractures, which are very much amenable to the
7 study in large data sets. For example, in the
8 Medicare data, there are well-established
9 algorithms for that. So it might also help
10 establishing the benefit, particularly for hip
11 fractures for this treatment.

12 DR. LEWIS: Thank you.

13 At this point, we are moving toward
14 adjournment. I'd like to thank all the panel
15 members for their participation, and the FDA staff,
16 as well as the sponsor.

17 Any last comments from the FDA?

18 DR. JOFFE: I'd like to thank everybody for
19 coming, and, Vivian, thank you for chairing this
20 meeting. And thank you, Amgen, for your
21 presentations as well. and I hope everybody gets
22 home safely.

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Adjournment

DR. LEWIS: Thank you. Panel members, please remember to take all your personal belongings with you. The room is cleaned at the end of the day, and materials or anything left will be disposed of. Please do leave your name badges on the table. They will be recycled. We are formally adjourned.

(Whereupon, at 4:00 p.m., the meeting was adjourned.)