

1 FOOD AND DRUG ADMINISTRATION

2 CENTER FOR DRUG EVALUATION AND RESEARCH

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4
5 ARTHRITIS ADVISORY COMMITTEE (AAC) MEETING
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10 MONDAY, MARCH 12, 2012

11 8:00 a.m. to 4:30 p.m.
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15 FDA White Oak Campus

16 White Oak Conference Center

17 Building 31, The Great Room

18 Silver Spring, Maryland
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22

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16 **(Non-Voting)**

17 **Richard Leff, M.D.**

18 ***(Acting Industry Representative)***

19 Independent Pharmaceutical Industry Consultant

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2 **Joan Bathon, M.D.**

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P R O C E E D I N G S

DR. BAUTISTA: Good morning. I would first like to remind everyone to please silence your cell phones, Blackberry, and other devices if you have not already done so. I'd also like to identify the FDA press contact, Morgan Liscinsky.

If you're present, please stand. Thank you.

Call to Order

Introduction of Committee

DR. BUCKLEY: Good morning. I would like to welcome everybody to the Arthritis Advisory Committee meeting today. We have an ambitious agenda. We're going to start this morning with introductions. We'll go around the table, go through those introductions.

I want to remind people at the table that you can turn your light on when you want to speak, and then to turn it off again as we go through the morning.

We'll start at this end of the table with Dr. Leff. If you would all introduce yourself and your affiliations, that would be great.

1 DR. LEFF: Yes. Hi. I'm Dr. Richard Leff.
2 I'm the industry representative today, and I'm an
3 independent consultant.

4 DR. BOTHWELL: Hello. I'm Mark Bothwell
5 from the University of Washington.

6 DR. GERSTENFELD: Louis Gerstenfeld from
7 Boston University.

8 DR. CLEMENS: Tom Clemens, Department of
9 Orthopedic Surgery, Johns Hopkins.

10 DR. HAQUE: Mustafa Haque, private practice,
11 orthopedic surgeon in Chevy Chase, Maryland.

12 DR. KELLY: John Kelly, IV, orthopedic
13 surgeon, University of Pennsylvania.

14 DR. KHURANA: Jasvir Khurana, pathologist at
15 Temple University.

16 DR. BOYCE: Brendan Boyce, pathologist at
17 the University of Rochester Medical Center in New
18 York.

19 MS. BROYLES: Susan Broyles, patient
20 representative from Fort Worth, Texas.

21 MS. COWAN: Penney Cowan, American Chronic
22 Pain Association.

1 DR. LAHITA: I'm Robert Lahita, chairman of
2 medicine at North Beth Israel Barnabas Health and
3 professor at University of Medicine and Dentistry
4 of New Jersey.

5 DR. NEOGI: Tuhina Neogi, rheumatologist and
6 epidemiologist from Boston University.

7 DR. MIKULS: Ted Mikuls, rheumatologist at
8 the University of Nebraska of Omaha and VA Medical
9 Center.

10 DR. BAUTISTA: Phillip Bautista, designated
11 federal officer for this committee.

12 DR. BUCKLEY: Lenore Buckley. I'm an adult
13 and pediatric rheumatologist at Virginia
14 Commonwealth University School of Medicine in
15 Richmond.

16 DR. BLUMENTHAL: David Blumenthal. I'm a
17 rheumatologist at Case Western Reserve University
18 and the Cleveland VA Medical Center.

19 DR. GABRIEL: Sherine Gabriel. I'm a
20 rheumatologist and epidemiologist from Mayo Clinic.

21 DR. SUAREZ-ALMAZOR: Good morning. I'm
22 Maria Suarez-Almazor. I'm a rheumatologist at MD

1 Anderson Cancer Center, University of Texas,
2 Houston.

3 DR. MORRATO: Good morning. I'm Elaine
4 Morrato. I'm an epidemiologist from the Colorado
5 School of Public Health at the University of
6 Colorado.

7 DR. BLOCK: I'm John Block. I'm a
8 radiologist at Vanderbilt University Medical Center
9 in Nashville, Tennessee.

10 DR. WALKER: Good morning. I'm Eric Walker.
11 I'm a radiologist at Milton S. Hershey Medical
12 Center.

13 DR. NEATON: Jim Neaton, a biostatistician
14 at the University of Minnesota.

15 DR. BILKER: Warren Bilker, biostatistician
16 from the University of Pennsylvania.

17 DR. FIELDS: Ellen Fields, FDA, division of
18 anesthesia, analgesia, and addiction products.

19 DR. HERTZ: Sharon Hertz, FDA, same
20 division.

21 DR. RAPPAPORT: Bob Rappaport, also from
22 that division.

1 DR. BUCKLEY: So to start, for topics such
2 as those being discussed at today's meeting, there
3 are often a variety of opinions, some of which are
4 quite strongly held.

5 Our goal is that today's meeting will be a
6 fair and open forum for discussion of these issues,
7 and that individuals can express their views
8 without interruption. Thus, as a gentle reminder,
9 individuals will be allowed to speak into the
10 record only if recognized by the chair. We look
11 forward to a productive meeting.

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

18 We are aware that members of the media are
19 anxious to speak with the FDA about these
20 proceedings. However, FDA will refrain from
21 discussing the details of this meeting with the
22 media until its conclusion.

1 Also, the committee is reminded to please
2 refrain from discussing the meeting topic during
3 the breaks or lunch. Thank you.

4 Now, Phillip Bautista will read the conflict
5 of interest statement.

6 **Conflict of Interest Statement**

7 DR. BAUTISTA: Thank you.

8 The FDA is convening today's meeting of the
9 Arthritis Advisory Committee under the authority of
10 the Federal Advisory Committee Act of 1972. With
11 the exception of the industry representative, all
12 members and temporary voting members of the
13 committee are special government employees or
14 regular federal employees from other agencies and
15 are subject to federal conflict of interest laws
16 and regulations.

17 The following information on the status of
18 this committee's compliance with the federal ethics
19 and conflict of interest laws, covered by but not
20 limited to those found at 18 U.S.C. Section 208 and
21 Section 712 of the Federal Food, Drug, and Cosmetic
22 Act, is being provided to participants in today's

1 meeting and to the public.

2 FDA has determined that members and
3 temporary voting members of this committee are in
4 compliance with the federal ethics and conflict of
5 interest laws. Under 18 U.S.C., Section 208,
6 Congress has authorized FDA to grant waivers to
7 special government employees and regular federal
8 employees who have potential financial conflicts,
9 when it is determined that the agency's need for a
10 particular individual's services outweighs his or
11 her potential financial conflict of interest.

12 Under Section 712 of the FD&C Act, Congress
13 has authorized FDA to grant waivers to special
14 government employees and regular federal employees
15 with potential financial conflicts when necessary
16 to afford the committee essential expertise.

17 Related to the discussion of today's
18 meeting, members and temporary voting members of
19 this committee have been screened for potential
20 financial conflicts of interest of their own, as
21 well as those imputed to them, including those of
22 their spouses or minor children, and, for purposes

1 of 18 U.S.C. Section 208, their employers. These
2 interests may include investments, consulting,
3 expert witness testimony, contracts, grants,
4 CRADAs, teaching, speaking, writing, patents and
5 royalties, and primary employment.

6 Today's agenda involves the discussion of
7 the anti-NGF drug class that is currently under
8 development and the safety issues possibly related
9 to these drugs. These drugs are being developed
10 for the treatment of a variety of chronic painful
11 conditions, including osteoarthritis, chronic lower
12 back pain, diabetic peripheral neuropathy,
13 post-herpetic neuralgia, chronic pancreatitis,
14 endometriosis, interstitial cystitis, vertebral
15 fracture, thermal injury, and cancer pain.

16 The committee will be asked to determine
17 whether ports of joint destruction represent a
18 safety signal related to the anti-NGF class of
19 drugs and whether risk-benefit balance for these
20 drugs favor continued development of the drugs as
21 analgesics.

22 This is a particular matters meeting during

1 which specific matters related to the anti-NGF
2 drugs will be discussed. Based on the agenda for
3 today's meeting and all financial interests
4 reported by the committee members and temporary
5 voting members, no conflict of interest waivers
6 have been issued in connection with this meeting.
7 To ensure transparency, we encourage all standing
8 committee members and temporary voting members to
9 disclose any public statements that they may have
10 made concerning the topic at issue.

11 With respect to FDA's invited industry
12 representative, we would like to disclose that
13 Dr. Richard Leff is participating in this meeting
14 as a non-voting industry representative, acting on
15 behalf of regulated industry. Dr. Leff's role at
16 this meeting is to represent industry in general
17 and not any particular company. Dr. Leff currently
18 works as an independent pharmaceutical industry
19 consultant.

20 We would like to remind members and
21 temporary voting members that if the discussions
22 involve any product or firm not already on the

1 agenda, for which the FDA participant has a
2 personal or imputed financial interest, the
3 participants need to exclude themselves from such
4 involvement, and their exclusion will be noted for
5 the record. FDA encourages all other participants
6 to advise the committee of any financial
7 relationships that they may have with the firm at
8 issue. Thank you.

9 DR. BUCKLEY: We have an ambitious agenda
10 today. We'll now proceed with Dr. Rappaport's
11 introductory remarks.

12 **FDA Introductory Remarks - Bob Rappaport**

13 DR. RAPPAPORT: Good morning.

14 Dr. Buckley, members, invited guests,
15 welcome to the FDA White Oak campus and to this
16 meeting of the Arthritis Advisory Committee.
17 Today's meeting will be somewhat unusual. The
18 majority of our advisory committee meetings are
19 public discussions intended to obtain expert advice
20 either for new drug product applications,
21 specifically regarding the appropriateness of
22 approving the application for marketing, or

1 regarding safety concerns that develop after a
2 product's approval.

3 It's less common for us to bring products
4 that are still under development before advisory
5 committees and even less common for us to bring
6 forward products that the agency has put on full or
7 partial clinical hold during phase 2 or 3 clinical
8 development.

9 Clinical hold is a regulatory term that you
10 will hear frequently today. It simply means that,
11 in the case of a full clinical hold, the drug
12 developers have been restricted from continuing to
13 administer to and study their drugs in human
14 subjects.

15 Partial clinical hold means that the drug
16 developers have been restricted from administering
17 study drug to a particular patient population or
18 that they have been restricted from administering a
19 particular dose or administering the drug over a
20 specific duration.

21 In most cases, clinical holds are
22 implemented in early development before clinical

1 studies have started because of incomplete non-
2 clinical evaluation, or due to toxicities noted in
3 animal studies where there is an inadequate margin
4 of safe exposure for humans, or because the
5 sponsors and/or investigators have not assured
6 adequate safety monitoring of subjects.

7 It is more unusual for the agency to put a
8 development program on clinical hold in later
9 stages of development when phase 2 and 3 clinical
10 studies are underway, as by that point in
11 development, the drug has already had extensive
12 animal evaluation to try to determine potential
13 safety issues, and the early phase 1 studies did
14 not demonstrate safety concerns.

15 However, occasionally unanticipated adverse
16 events occur frequently enough that they are
17 detected at this stage. And when a signal of
18 potentially significant toxicity does appear in
19 phase 2 or 3, and the risk associated with that
20 toxicity is not clearly outweighed by the benefit
21 of the drug for a particular patient population, we
22 are obligated to place the studies on clinical hold

1 as we attempt to better understand the true nature
2 of the risk, the potential benefit, and the balance
3 of the risk and benefit for the subjects in
4 clinical trials.

5 In this case, a signal of severe, rapidly
6 progressive, and painful arthropathy leading to
7 joint destruction and requiring joint replacement
8 appeared during later-stage clinical trials, first,
9 in one of the three agents under discussion today.
10 These events occurred in the subjects exposed to
11 the active agent and not in the subjects
12 administered placebo.

13 The first events were reported by Pfizer in
14 April of 2010. Additional data were requested of
15 the sponsor. And after a review of those data, the
16 tanezumab osteoarthritis and chronic low back pain
17 studies were placed on clinical hold.

18 In December of 2010, cases with fulranumab
19 were noted by Janssen. This caused us to suspect
20 that these adverse events may be a class effect of
21 the anti-NGF agents, and all active INDs were
22 placed on hold with the exception of a single study

1 in terminal cancer patients with severe pain from
2 bone metastases, a population of patients for whom
3 the currently available analgesic therapies are
4 often inadequate and the benefit was thought to
5 outweigh the risk.

6 A meeting of the Arthritis Advisory
7 Committee was initially scheduled for September of
8 2011, but Pfizer and Janssen submitted their
9 responses in support of removing the clinical holds
10 just a couple of months before the scheduled
11 meeting. These responses included hundreds of
12 cases. And in order to perform an adequate review
13 of the large quantity of data submitted to us, we
14 had no choice but to postpone the advisory
15 committee meeting until March.

16 The cases of arthropathy requiring joint
17 replacement were reviewed by a committee of
18 consultants for Pfizer. Their consultant committee
19 attempted to make a diagnosis for these cases and
20 to determine which events were possibly related to
21 product exposure and which were not.

22 Initially, Pfizer and their consultants

1 concluded that there was no signal for abnormal
2 arthropathic events. However, as additional data
3 became available after the clinical hold was
4 implemented and as cases were identified for more
5 than one anti-nerve growth factor agent, they
6 changed their conclusions to agree that there was,
7 indeed, a signal. Also, Janssen had their own
8 consultants adjudicate the data from their studies.

9 In light of the sponsors' adjudications and
10 in order to assure a balanced presentation of the
11 data for you today, the division obtained
12 adjudications from two additional consultants.

13 First, Dr. Nona Colburn, a rheumatologist
14 with additional training in orthopedic surgery and
15 a medical officer in the Agency Center for Devices
16 and Radiologic Health, performed a blinded
17 adjudication of all of the data received by the
18 division. As a full-time FDA employee, Dr. Colburn
19 was able to review the same data, including the
20 electronic MRIs and histopathology that the
21 sponsors' consultants reviewed.

22 Our second adjudicator was Dr. Joan Bathon,

1 professor of medicine and the director of the
2 division of rheumatology at Columbia University.
3 Additionally, some of Dr. Bathon's colleagues at
4 Columbia reviewed the case reports, the radiologic
5 findings, or the pathology data, and provided her
6 with breakdowns of the results by blinded case
7 number.

8 Dr. Bathon then adjudicated each case while
9 maintaining the blind. We then provided her with
10 the subject assignment data and she compared her
11 blinded adjudication to the sponsors' experts'
12 adjudications.

13 You have seen the results of both
14 Dr. Colburn's and Dr. Bathon's analyses in the
15 addenda to the background package that you received
16 for this meeting, and they will each be presenting
17 their work to you later today.

18 In order to achieve a reasonable balance
19 between providing the committee with appropriately
20 reviewed data and not keeping these developed
21 programs on clinical hold any longer than was
22 absolutely necessary, certain limitations in the

1 performance of our reviews exist.

2 Specifically, for the Columbia team's work,
3 it's important to note that due to time constraints
4 and the difficulties associated with the clearance
5 process for external consultants, they did not have
6 access to the electronic MRI and histopathology
7 data, and they were limited to reviewing crude
8 paper copies and narrative reports.

9 Nevertheless, even with the limitations
10 involved in these reviews, the severe time
11 constraints, and the small differences in the
12 adjudication protocols between Drs. Colburn and
13 Bathon and the sponsors' adjudicators, we believe
14 that these efforts were successful and that they
15 will provide you with very helpful information in
16 determining the best path forward.

17 It will be clearly important to fully
18 understand the pathophysiology of these events,
19 which may well help provide a means to mitigate the
20 risk and allow development of these agents to move
21 forward. However, as a first-level evaluation of
22 whether to allow continued clinical study, we

1 charged our consultants with the primary task of
2 determining whether these rapidly progressive
3 arthropathies, whatever the underlying
4 pathophysiology may be, are unexpected for the
5 patient populations in the clinical studies or
6 whether they are occurring at a frequency that is
7 higher than expected in this population.

8 The sponsors and the agency agree that these
9 arthropathic events are associated with exposure to
10 the anti-nerve growth factor agents. Therefore,
11 the most important questions for us today are,
12 first, do you agree that these events are related
13 to exposure to these agents? And second, do you
14 believe that their occurrence in the setting of
15 anti-nerve growth factor antibody exposure is also
16 correlated with underlying osteoarthritis and/or
17 with concomitant exposure to NSAIDs?

18 The answers to these questions will lead us
19 to the even more challenging question of whether to
20 allow continued clinical study of these agents; and
21 if so, in what disease states or patient
22 populations.

1 Considering the rapidly progressive nature
2 of these severe adverse events and the lack of
3 clarity regarding the pathophysiological mechanism
4 that is causing them, it is simply not possible to
5 assure that subjects can be monitored for early
6 signs of pain or radiographic changes that will
7 allow prevention of the development of joint
8 destruction.

9 Thus, the key deliverable that we are hoping
10 to receive from you today is your advice regarding
11 the appropriate direction for the sponsors'
12 development programs. In which patient
13 populations, if any, would it be acceptable to
14 continue to study these agents? If the study
15 populations should be restricted, to what disease
16 states or patient populations should they be
17 limited?

18 If your suggestion is to limit exposure,
19 examples could be to those with severe refractory
20 pain or to a more restrictive setting such as
21 terminally ill cancer patients.

22 We also will ask if there are additional

1 non-clinical studies that should be undertaken in
2 order to consider future investigations in less
3 restricted populations.

4 As the division that reviews 99 percent of
5 the analgesic drug products, we are acutely aware
6 of the unmet need for better analgesic therapies
7 and we have been and will continue to strongly
8 encourage the development of safer, more effective,
9 novel analgesics.

10 These analgesic agents may hold promise, but
11 it is critically important to carefully consider
12 these benefits in light of the associated risks,
13 and the fact that it may not be possible to monitor
14 and prevent progression of these arthropathic
15 events, and to use discretion and caution in
16 recommending a path forward.

17 For that reason, your discussions and
18 recommendations today will be taken into
19 consideration and help to guide us in our ultimate
20 decisions regarding these development programs. We
21 thank you for sharing your time and expertise to
22 help us make fair, well-informed, and well-reasoned

1 decisions.

2 Before I turn the meeting back to
3 Dr. Buckley, I'd like to thank some of the people
4 who assisted the division in preparing for this
5 meeting.

6 First, Dr. Janet Maynard is a medical
7 officer and rheumatologist in our sister division,
8 the Division of Pulmonary, Allergy, and
9 Rheumatology Products. Dr. Maynard will be
10 providing you with an overview of the natural
11 history of osteoarthritis and the potential
12 clinical causes of joint destruction that I think
13 you will find particularly helpful in putting the
14 data into perspective. Dr. Maynard put many hours
15 of effort into preparing this presentation, far
16 above and beyond her regularly assigned duties.

17 Dr. Colburn also spent innumerable hours
18 working on her adjudication of the cases for us and
19 preparing a presentation for you while holding down
20 her full-time job and all of the associated
21 responsibilities over in CDRH.

22 I thank both Drs. Maynard and Colburn, and

1 I'd like to also thank their team leaders and
2 division directors for being willing to share these
3 outstanding agency experts with us.

4 Finally, to the folks from Columbia, in
5 particular Dr. Bathon, we are enormously grateful
6 for their time and effort. I don't think they had
7 any idea of what they were getting themselves into
8 when they agreed to take this project on. But they
9 did an outstanding job under difficult
10 circumstances, as I think will be apparent to you
11 today.

12 So thank you all very much.

13 DR. BUCKLEY: Thank you, Dr. Rappaport.

14 We are going to now move on to the sponsors'
15 presentation.

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

1 For this reason, FDA encourages all
2 participants, including the sponsor's non-employee
3 presenters, to advise the committee of any
4 financial relationships that they may have with the
5 firm at issue, such as consulting fees, travel
6 expenses, honoraria, and interest in the sponsor,
7 including equity interests, and those based on the
8 outcome of the meeting.

9 Likewise, FDA encourages you, at the
10 beginning of your presentation, to advise the
11 committee if you do not have any such financial
12 relationships. If you choose not to address this
13 issue of financial relationship at the beginning of
14 your presentation, it will not preclude you from
15 speaking.

16 I will now proceed with the sponsor's
17 presentation. I think we have Dr. Verburg.

18 We'll start with Dr. Rosenberg [sic].

19 **Industry Presentation - Ken Verburg**

20 DR. VERBURG: Good morning. My name is Ken
21 Verburg, and I'm the team leader for the tanezumab
22 development program at Pfizer. On behalf of Pfizer

1 and the other sponsors, Janssen R&D and Regeneron,
2 I would like to start with thanking the FDA for
3 convening the meeting and thanking the members of
4 the Arthritis Advisory Committee for their
5 preparation and participation in the meeting today.

6 In what may be an unprecedented effort for
7 agents that do not yet have marketing approval, the
8 sponsors have worked together for over a year now
9 to share information and analyses of their
10 respective development programs to reach a common
11 understanding of the safety events that resulted in
12 the partial clinical hold for the anti-nerve growth
13 factor monoclonal antibodies. And we are pleased
14 to have the opportunity to meet with the Arthritis
15 Advisory Committee today to share our results.

16 So the narrative or subtext for today's
17 meeting is that, first, the anti-NGF monoclonal
18 antibody development programs and the regulatory
19 process worked. A safety signal was identified
20 prior to marketing approval. The signal was not
21 predicted by six decades of research on nerve
22 growth factor, and so a cautionary response was

1 taken. It turns out the concern was justified,
2 although it was later learned the initial
3 description of the event as osteonecrosis was
4 incorrect.

5 Based on careful assessment, and
6 corroborated across separate analyses by Pfizer-
7 Janssen, the safety issue at hand is rapidly
8 progressive osteoarthritis. Importantly, careful
9 examination of the data has allowed for
10 identification of measures that would reduce the
11 risk by 90 percent in future clinical trials.

12 So our understanding of this situation has
13 evolved substantially since the programs were put
14 on clinical hold. And so today, we are, for all
15 intents and purposes, at an important crossroads
16 with fundamental questions to be addressed, whether
17 to resume development of the anti-NGF therapies,
18 and, if so, how best to proceed.

19 I think it's safe to say that this meeting
20 would not be taking place if the efficacy profile
21 of the anti-NGF therapies was no better than
22 current therapies for chronic pain. However, the

1 evidence is that anti-NGF therapies hold the
2 promise of bringing a step-change to the treatment
3 of chronic pain. And there is a need for further
4 studies to examine and demonstrate the
5 effectiveness of this therapeutic approach.

6 As we all know, the opportunities to advance
7 the treatment of pain have been very limited.
8 Despite decades of research, we've not seen any
9 compounds in the clinic with similar efficacy
10 characteristics to those of the anti-NGF therapies.

11 There are many examples one could show to
12 illustrate the therapeutic potential of NGF
13 inhibition. The concepts for the results I am
14 showing on this slide are quite simple. In the
15 most basic sense, when all of us take a drug for
16 pain, we want the pain to be gone, and we want to
17 be able to care on our daily activities, not just
18 reduced by one or two points on a pain severity
19 measure.

20 As shown on this slide, nearly 1 in 3
21 patients with osteoarthritis and treated with
22 tanezumab in a phase 3 clinical program reported

1 minimal to no pain over a sustained period of time
2 during treatment. As evidenced by the baseline
3 scores shown along the bottom of this graph, these
4 were patients who on average were experiencing
5 nearly severe pain.

6 The results are even more impressive when we
7 ask the same question about only those patients who
8 are experiencing severe osteoarthritis pain prior
9 to receiving study medication. That is, these are
10 patients with pre-treatment pain scores above 7 on
11 a zero to 10 point numerical rating scale. We see
12 that nearly one-third of these patients also report
13 little to no pain when treated with tanezumab.

14 Indeed, this is why the sponsors and the
15 clinical investigators who have treated patients
16 with tanezumab and other NGF inhibitors, and many
17 of the patients who participated in the clinical
18 studies, are so enthused about the potential of
19 this therapeutic approach.

20 The intent of the sponsor presentations this
21 morning is to briefly summarize the available
22 information regarding the effects of anti-NGF

1 therapies on joints and the efficacy results
2 collected to date. In addition, we will propose
3 additional measures that would be taken to optimize
4 the benefit and reduce the risk, further protect
5 patient safety, and provide safe conduct of
6 clinical studies going forward.

7 In doing so, we are seeking confirmation
8 from the Arthritis Advisory Committee that clinical
9 development of anti-NGF monoclonal antibodies
10 should resume; secondly, that the sponsor's
11 proposed measures to minimize the risk, protect
12 patient safety, and to characterize the risk
13 further are sufficient and that the chronic pain
14 conditions selected in the studies proposed are
15 acceptable approaches for re-initiating the
16 clinical programs.

17 The organization of our presentations are
18 outlined on this slide. Dr. Tom Schnitzer, a
19 rheumatologist by training and professor of
20 medicine at Northwestern University, will lead off
21 by providing his perspectives on chronic pain.
22 Dr. Schnitzer was also investigator in several

1 clinical trials with tanezumab and has firsthand
2 experience in administering this therapy to
3 patients.

4 Dr. Schnitzer's presentation will be
5 followed by presentations by the sponsor specific
6 to each compound. And finally, these presentations
7 will be followed by some concluding remarks
8 provided by Dr. Nat Katz, president of the
9 consulting firm Analgesic Solutions and assistant
10 professor at Tufts University.

11 We are pleased to be joined here today by a
12 delegation of external experts who are recognized
13 authorities across a range of medical specialties,
14 including orthopedic surgery, pathology,
15 rheumatology, neurology, radiology, and
16 pharmacology. Many of these individuals served on
17 the Pfizer or Janssen adjudication committees
18 and/or have been scientific advisors for one or
19 more of the anti-NGF programs for several years, in
20 some instances, dating back to a time when these
21 compounds were still in the pre-clinical testing
22 stage.

1 These individuals are available to describe
2 their work with anti-NGF therapies and to answer
3 any questions the committee may have through the
4 course of the day. Thank you very much.

5 Dr. Schnitzer?

6 **Industry Presentation - Tom Schnitzer**

7 DR. SCHNITZER: Good morning.

8 Dr. Buckley, members of the committee,
9 members of the FDA, ladies and gentlemen. First,
10 in light of full disclosure, let me say that I have
11 been paid an honorarium for my time in preparing
12 for this meeting and for travel expenses for the
13 meeting. This presentation was put together
14 entirely by me with the exception of some data
15 which I received from the sponsors in regard to
16 their products.

17 So for the next approximately 15 minutes,
18 before we get into a discussion of the research
19 data, I'd like to focus on providing a clinical
20 perspective on the current status of chronic pain
21 management and what needs we still have. I will
22 start by presenting epidemiologic data,

1 highlighting the prevalence and impact of chronic
2 pain, then explore the basis of our current
3 limitations in the treatment of chronic pain, and
4 end by discussing why inhibiting NGF activity could
5 represent a major advance.

6 Portions of the data I'll be referencing
7 data are included in a report published by the
8 Institute of Medicine late last year and generated
9 by a committee specifically organized to study and
10 report on pain management in the U.S. today.

11 The report estimates conservatively that
12 there are at least 116 million individuals
13 suffering from chronic pain in the United States.
14 Most have pain secondary to musculoskeletal
15 conditions, of which OA and back pain are the most
16 common.

17 However, it's very important to point out,
18 particularly to my rheumatology colleagues on the
19 panel, that there are millions of other Americans
20 with chronic pain that we generally, as
21 rheumatologists, don't see or treat. These are
22 people with neuropathic pain, with visceral pain,

1 with central pain syndromes, conditions for which
2 we have treatments with marginal efficacy or no
3 treatments whatsoever.

4 Now, chronic pain, when we discuss it, is
5 clearly impactful first and foremost on people
6 themselves. As this quote taken from the IOM
7 report states, "Pain is more than 7 out of 10 on a
8 visual analog scale. It impacts people's ability
9 to work, to engage in recreational and social
10 activities, and for some, perform the most basic
11 everyday activities that people just take for
12 granted."

13 Not surprisingly, pain begins to chip away
14 at their mood, often leaving them angry,
15 frustrated, anxious, and depressed. Our families
16 suffer along with us and many relationships are
17 forever altered. Thus, chronic pain impacts
18 quality of life and well-being, affects function
19 and ability, and has medical and economic
20 consequences.

21 So I'd like to focus on each of these just
22 briefly. A number of studies have examined the

1 impact of chronic pain on quality of life, and the
2 data here on the left demonstrate that across
3 multiple domains measuring physical and mental
4 well-being, using the SF36 instrument, there is a
5 marked reduction in all areas, compared to the
6 normative value shown in this slide by the dots
7 above the bars. And this study depicted on the
8 right points out the close relationship between
9 severity of pain and functional limitations so that
10 mild pain produces changes in emotional responses,
11 but greater degrees of pain can have a major impact
12 on function, including ability to work and walking.

13 Other studies have specifically examined the
14 effects of pain on function. The results shown
15 here on the left of this slide come from the
16 National Health Interview Survey and then
17 demonstrate that among individuals responding that
18 they had chronic back pain or joint pain during the
19 past three months; anywhere from one-third to
20 one-half had pain-related disability in self-care,
21 work, or social spheres.

22 These limitations in function have also been

1 directly linked to an increase in mortality. A
2 recent study by Paul Dieppe's group from the U.K.,
3 shown on the right, demonstrates that OA patients
4 with disability had a marked increase in all-cause
5 mortality over a 15-year follow-up, compared to OA
6 patients without disability.

7 So this is an effect clearly on something
8 other than simply pain, but really on mortality
9 itself and life expectancy.

10 The economic consequences of pain-related
11 disability are substantial. The IOM-published
12 report estimates that the total annual economic
13 cost at approximately \$600 billion annually is
14 fairly evenly split between direct medical
15 expenses and costs due to decreased productivity.
16 Of total Medicare expenditures, 65 billion or
17 14 percent, \$1 out of every \$7 goes towards care
18 for pain, and other federal agencies then have
19 added another 30 billion in expenditures on pain.

20 These are all considered conservative
21 estimates, as they don't include expenditures on
22 individuals residing in long-term care facilities,

1 in prisons, and the military.

2 So in summary, I think chronic pain is
3 common. It has major impacts on people's lives in
4 many domains and is clearly costly to patients and
5 to society. While preventing the onset of chronic
6 pain may be challenging, what is true and is
7 underscored by the IOM report is that management of
8 chronic pain often fails. Failure occurs for a
9 variety of reasons, because of systemic
10 deficiencies in our healthcare delivery system, a
11 failure of education of our healthcare providers,
12 and also because of the need for more effective
13 therapies.

14 In regard to the latter, the IOM report
15 states, "Academia and industry should develop novel
16 agents for the control of pain. This does not mean
17 simply recycling current drugs. What is required
18 is basic and clinical science research to discover
19 new classes of pain therapeutics and more efficient
20 ways of developing them."

21 So I'd like to turn now to how we manage
22 chronic pain today, and let me focus on

1 musculoskeletal pain because as a rheumatologist,
2 that's really what I know most about.

3 NSAIDs and opioids are the most widely-used
4 drug classes in musculoskeletal pain. With regard
5 to non-steroidals, these drugs have modest
6 efficacy. To evaluate efficacy, I've turned
7 primarily to published studies from the Cochrane
8 Database of Systematic Reviews, as these are
9 generally accepted as high quality and rigorous
10 methodology.

11 Acetaminophen, in the upper left graph, is
12 considered first-line treatment for OA by the
13 American College of Rheumatology and by
14 international guidelines. The systematic review,
15 and meta-analysis by Towheed -- and again, the data
16 shown in the upper left -- provides an estimated
17 effect size of 0.13, which although statistically
18 significantly different from placebo, is not said
19 in that review to reach a clinically significant
20 threshold for providing pain relief.

21 NSAIDs have a standardized mean difference
22 of approximately 0.3, which lies in the small or

1 modest range, both statistically and clinically
2 significant. And opioids at doses used to treat
3 musculoskeletal pain have a similar effect size.
4 So all in all, there's at least modest efficacy
5 with all existing approaches to pain management in
6 musculoskeletal conditions.

7 These data help explain the fact,
8 demonstrated in the graph below, that only
9 approximately half of the people starting or
10 requiring an NSAID for OA remain on the same
11 medication for more than three months and fewer
12 than 20 percent will be expected to take that agent
13 at one year. Marginal and waning efficacy as well
14 as issues with tolerability have been well-
15 documented with all non-steroidal anti-inflammatory
16 drugs.

17 If we now turn to examining the safety of
18 the pharmacologic options, starting with NSAIDs, I
19 don't need to remind this panel of the several
20 decades of discussions we've had relating first to
21 gastrointestinal safety and more recently to
22 cardiovascular safety concerns regarding

1 non-steroidal anti-inflammatory drugs.

2 Rather than present selected data from this
3 literature, suffice it to say that the tangible
4 results of these studies and the meetings with the
5 FDA is expressed in an NSAID, class-based box
6 warning for both of these areas, as shown in the
7 slide on the right and naproxen product.

8 Opioids are the other major pharmacologic
9 agent used to treat musculoskeletal pain. And
10 again, we're well aware of the myriad limiting side
11 effects of treatment. Constipation is almost
12 universal. Sedation, drowsiness, and cognitive
13 impairment occur often. And dizziness, often
14 resulting in falls, is a common accompaniment.

15 In an informative article published by
16 Solomon and his group, they examined the occurrence
17 of fractures after the onset of opioid therapy for
18 people specifically with arthritis.

19 Drawing data from the link, clinical and
20 administrative database, the report has
21 significantly elevated hazard rate for fractures in
22 a population of older individuals with arthritis

1 beginning opioid therapy compared to those
2 initiating NSAIDs, with the increased incidence
3 being greatest in the initial two weeks after
4 starting treatment and being disproportionately
5 focused on short-acting opioids, the most widely
6 used typed for musculoskeletal pain. And that's
7 demonstrated on the graph on the right.

8 Clearly, there's a need for better pain
9 medications, and this fact has not been lost on all
10 the interested parties. During the past 20 years,
11 there's an explosion of knowledge regarding pain,
12 including better definitions of neuropathways
13 involving pain, as well as the neurobiology of pain
14 itself.

15 A host of neurotransmitters and their
16 receptors have been better defined. Many of these
17 have served as clear targets for drug development
18 by the PhRMA industry. The list in the middle of
19 the slide represents only a partial summary of the
20 drug targets that have been or are under
21 development. However, despite what has been an
22 enormous effort by not only industry, but also by

1 government and academia, there has been a paucity
2 of new agents for pain. To get one perspective of
3 the current status, I turned to the
4 clinicaltrials.gov website prior to this meeting.

5 There were 539 active trials listed with
6 chronic pain as an indication. Among these, there
7 are only eight studies of new molecular entities,
8 and only two of which are focused on
9 musculoskeletal pain. What I believe this reflects
10 is a failure of many drugs in early phase 1
11 proof-of-concept studies, which often are not
12 listed, and very few viable candidates that make it
13 to phase 2 and beyond.

14 In that context, with that as background,
15 let's turn to NGF, the topic of our discussion
16 today. NGF was first identified as important in
17 pain over 10 years ago. It was recognized that an
18 injection of NGF in animals and in man resulted in
19 pain, that NGF was up-regulated locally in painful
20 conditions, and that blocking NGF in animals was
21 shown to prevent responses to otherwise painful
22 stimuli. This resulted in the development of

1 monoclonal antibodies specifically directed toward
2 inhibiting NGF and then testing these in man, which
3 brings us to today's meeting.

4 Three different monoclonal antibodies are
5 the focus of today's meeting, tanezumab,
6 fulranumab, and RGN475. These all have high
7 affinity and specificity for NGF and inhibit NGF
8 activity at both the TrkA and P75 receptors.
9 They've been evaluated in clinical programs with
10 different dosing regimens, different routes of
11 administration, and different doses.

12 What has been remarkable about these agents
13 is that efficacy has been demonstrated in a wide
14 range of different pain states. Clearly effective
15 in osteoarthritis and back pain, with positive
16 results in diabetic neuropathic pain, and possibly
17 effective in other neuropathic and visceral pain
18 conditions, these latter studies have all been
19 either small trials or interrupted by the clinical
20 hold requested by the FDA; so additional studies
21 are clearly needed before it's clear regarding
22 possible efficacy. Trials in cancer pain, as you

1 heard, are ongoing.

2 Two points to make that are noteworthy.
3 First, it's remarkable to have a class of drugs
4 that shows efficacy in both nociceptive and
5 neuropathic pain studies. And secondly, the
6 magnitude of efficacy seen with tanezumab in OA and
7 back pain, as you've heard, and will hear about
8 further, was greater than the active comparator,
9 which again is unprecedented in these types of pain
10 studies.

11 If we turn to the safety and examine the
12 safety finding from these trials to date, there are
13 no data suggesting any GI or cardiovascular
14 concerns, nor have any increased frequency of
15 opioid-like adverse events been reported. However,
16 there has been an increase in joint-related adverse
17 events, which is what has brought us to this
18 meeting.

19 So the committee will clearly be grappling
20 with a number of questions. What does this safety
21 signal represent? Under what conditions does this
22 signal occur, and at what frequency? And is it

1 advisable to undertake further research with these
2 compounds to define better the benefit risk?

3 So I'd like to end with a thought that the
4 anti-NGF approach to pain management is the first
5 new treatment to have reached this stage in many
6 years. It's notable for the degree of pain relief
7 observed and, perhaps equally importantly, for the
8 breadth of possible clinical conditions for which
9 it may work.

10 Given these findings, it's absolutely
11 essential that research with these compounds
12 progress, as this is the only way we can learn how
13 to use them appropriately, that is, in what
14 population of patients, with what concomitant
15 medications, at what dose, and for how long.

16 We owe it to the many people suffering from
17 chronic pain, not only osteoarthritis, but also
18 neuropathic pain, visceral pain, and central pain,
19 conditions for which we have limited or no
20 effective therapies, to not cut off research
21 prematurely.

22 The decision today is not about whether any

1 of these products should be approved for marketing,
2 but rather whether these agents can and should be
3 studied in carefully designed trials with
4 well-defined populations who have been fully
5 informed and provided consent and after
6 incorporation of appropriate risk mitigation steps.

7 We need to learn more about these agents,
8 their efficacy in various conditions, and their
9 safety. I'm confident this can be done in a
10 responsible manner with the input from this
11 committee, from the FDA, and from the sponsors
12 present today. Thank you very much for your
13 attention.

14 **Industry Presentation - Ken Verburg**

15 DR. VERBURG: For the next 45 minutes or so,
16 I'm going to work my way through the results of the
17 tanezumab program. I'm going to start here, and
18 the key points I'd like to bring forward in my
19 presentation are as follows.

20 First, tanezumab relieves pain and improves
21 function to a clinically meaningful extent across
22 chronic pain conditions, as you've now heard

1 several times, and is superior to active
2 comparators in the treatment of osteoarthritis and
3 chronic low back pain.

4 Secondly, tanezumab monotherapy does not
5 elevate the risk of all-cause total joint
6 replacements and this is in contrast to when
7 tanezumab is administered with non-steroidal
8 anti-inflammatory drugs.

9 Adjudication of the total joint replacements
10 showed tanezumab does not elevate the risk of
11 osteonecrosis, but rather is associated with a
12 dose-related increase in rapidly progressive
13 osteoarthritis, which is further increased by
14 threefold or greater when administered with NSAIDs.

15 Finally, risk minimization procedures should
16 reduce the risk of rapidly progressive
17 osteoarthritis in future clinical trials.

18 So this is the first of three slides
19 intended to provide some background on the
20 tanezumab clinical development program before we
21 move directly into a discussion of the results.
22 The clinical program can be subdivided into three

1 components based on the stage of development.

2 Tanezumab was in phase 3 development for
3 moderate to severe osteoarthritis and was being
4 examined as both monotherapy and in combination
5 with NSAIDs at doses of 2.5, 5, and 10 milligrams,
6 administered every eight weeks. Tanezumab was in
7 phase 2 development for moderate to severe chronic
8 low back pain as monotherapy at doses of 5, 10, and
9 20 milligrams every eight weeks. And finally,
10 tanezumab was in early clinical development testing
11 for other chronic pain conditions, including
12 neuropathic, visceral, and cancer pain as
13 monotherapy or as an adjunctive therapy with
14 standard of care at doses of up to 20 milligrams.

15 Thirty clinical studies involving over
16 11,000 study participants have been conducted with
17 tanezumab to date. In keeping with the description
18 of the program on the previous slide, over one-half
19 of these studies were conducted in patients with
20 osteoarthritis, and in turn, the majority of these
21 studies comprised the phase 3 development program.

22 Three phase 2 studies have been conducted in

1 patients with chronic low back pain, and the
2 remaining 10 studies have been conducted in chronic
3 pain conditions other than osteoarthritis, or
4 chronic low back pain, or in healthy volunteers.

5 Of the 11,000 patients randomized and
6 treated in the completed clinical studies, over
7 1600 were treated with placebo, with exposure for
8 up to six months. Over 6400 were treated with
9 tanezumab monotherapy, with exposure up to
10 two years; 3400 patients were treated with
11 tanezumab in combination with NSAIDs, with exposure
12 up to two years. And it's important to emphasize
13 this includes patients randomized to combination
14 therapy and concomitant NSAID use in long-term,
15 non-controlled studies.

16 Finally, over 1600 patients were treated
17 with active comparators, including naproxen,
18 celecoxib, diclofenac sustained release, and
19 oxycodone controlled release, for periods of up to
20 1 year.

21 So in terms of the overall duration of
22 exposure, over 5,000 patients were treated with

1 tanezumab for six months or longer, and nearly
2 1,000 patients were treated for one year or longer
3 at the time of the clinical hold.

4 So my presentation is organized into the
5 topics of efficacy, joint safety, and risk
6 minimization, beginning with efficacy, and
7 specifically the efficacy in patients with
8 osteoarthritis.

9 So the four controlled studies in patients
10 with knee or hip osteoarthritis, shown in the left-
11 hand column of this slide, were completed before
12 the clinical hold took effect. Each of these
13 studies had three co-primary outcome measures, the
14 WOMAC pain subscale, the WOMAC physical function
15 subscale, and the patient's global assessment of
16 osteoarthritis, with the landmark analysis after
17 16 weeks of treatment.

18 The statistical comparisons of tanezumab to
19 placebo for these three co-primary outcomes are
20 summarized in this slide. Tanezumab at doses of
21 2.5 to 10 milligrams provided consistently superior
22 efficacy over placebo treatment across all efficacy

1 measures in all four studies. And these are not
2 the results we are accustomed to seeing with many
3 other analgesics.

4 So the WOMAC pain categorical responder
5 rates, ranging from at least 30 percent to a high
6 of at least 90 percent, from one of the two
7 placebo-controlled studies that included the
8 tanezumab 2.5-milligram dose, is shown here.

9 The percentage of patients treated with all
10 doses of tanezumab exceed placebo treatment, yet
11 all response levels, including 90 percent, are
12 greater. Note that the percentage of responding
13 patients were similar with tanezumab 5 and 10
14 milligrams, which in turn were somewhat greater
15 than with tanezumab 2.5 milligrams.

16 So the benchmark for tanezumab efficacy in
17 the phase 3 program was not comparisons to placebo,
18 but rather comparisons to active treatments. These
19 were three studies in the phase 3 osteoarthritis
20 program that directly compared tanezumab 5 or
21 10 milligrams to NSAID treatment. In two studies,
22 comparisons were made against naproxen. And in the

1 third study, comparisons were made to both naproxen
2 and to celecoxib. The primary landmark analysis
3 was prespecified at week 16 of treatment for these
4 studies, and the analyses were not impacted by the
5 clinical hold.

6 As is evident from the slide, tanezumab
7 5 milligrams provided significantly greater mean
8 reduction in pain for the four comparisons across
9 all three studies, and tanezumab 10 milligrams for
10 both comparisons in one study.

11 Significant improvements in the WOMAC
12 physical function over NSAIDs were observed in all
13 comparisons versus placebo, and significant mean
14 treatment differences proved to be more difficult
15 to demonstrate on a consistent basis with the
16 patient's global assessment efficacy measure.

17 So the WOMAC pain categorical responder
18 rates, ranging from at least 30 to a high of at
19 least 90 percent from one of these three active
20 control studies, is shown here. With the exception
21 of tanezumab 10 milligrams at the 30 percent
22 responder level, the percentage of patients treated

1 with both doses of tanezumab exceeded naproxen
2 treatment at all response levels, including, again,
3 90 percent or greater. Here again, we see that the
4 percent of responding patients were generally
5 similar with tanezumab 5 and 10 milligrams.

6 The efficacy results shown on this slide are
7 from a phase 3 study of the efficacy of tanezumab
8 in patients, again, with osteoarthritis of the hip
9 or knee, in comparison to placebo, or in this
10 instance, oxycodone controlled release.

11 The study was discontinued prematurely due
12 to the clinical hold and only 62 percent of the
13 planned enrollment was achieved. And as a result,
14 the landmark analysis was amended prior to study
15 unblinding from week 16 to 8 weeks of treatment.

16 Tanezumab 5 and 10 milligrams produced
17 comparable and significantly greater improvement
18 compared to placebo and oxycodone controlled-
19 release treatment in the WOMAC pain subscale, as
20 well as the physical function subscale and the
21 patient's global assessment.

22 Now, moving on to chronic low back pain,

1 we've completed two studies in patients with this
2 condition. Both studies demonstrated tanezumab
3 provides significantly greater efficacy than either
4 placebo or naproxen. The results from the largest
5 of these two studies is shown on this slide.

6 Tanezumab, 10 and 20 milligrams, provided
7 significant improvement in pain, in function, and
8 in overall global well-being compared to either
9 placebo or naproxen treatment. The efficacy
10 results with tanezumab in patients with chronic low
11 back pain are among the best we've seen for any
12 agent in this condition. In most instances, the
13 treatment effects are modest at best.

14 We've also conducted two early studies
15 examining the efficacy of tanezumab in conditions
16 of neuropathic pain, specifically patients with
17 diabetic peripheral neuropathy or patients with
18 post-herpetic neuralgia. There were indications of
19 an efficacy response to treatment with tanezumab in
20 both conditions and particularly so in diabetic
21 peripheral neuropathy.

22 We've also conducted two early studies in

1 conditions of visceral pain, patients with
2 interstitial cystitis or patients with chronic
3 prostatitis. Both are difficult-to-treat chronic
4 pain conditions and are not well-studied, as
5 evidenced by the low number of studies reported in
6 the literature. Again, there were indications of
7 an efficacy response in both conditions and
8 particularly so in interstitial cystitis.

9 So to summarize, in the treatment of
10 osteoarthritis, tanezumab monotherapy has superior
11 efficacy compared to placebo and NSAIDs and a
12 favorable efficacy profile compared to oxycodone
13 controlled release, based on preliminary data.
14 Minimal incremental benefit of
15 tanezumab 10 milligrams versus 5 milligrams is
16 observed, and tanezumab 2.5 and 5 milligrams are
17 emerging as appropriate therapeutic doses for
18 osteoarthritis.

19 In the treatment of chronic low back pain,
20 tanezumab 10 and 20 milligrams have shown superior
21 efficacy compared to placebo and naproxen. The
22 evidence indicates there is minimal incremental

1 benefit of tanezumab 20 milligrams versus the lower
2 dose of 10 milligrams in the treatment of this
3 condition. And finally, there is preliminary
4 evidence of analgesic efficacy with tanezumab at
5 doses of 20 milligrams in neuropathic and visceral
6 pain.

7 My presentation on joint-related safety is
8 subdivided into two topics. The first is a
9 description of total joint replacements for any
10 cause, and the second topic focuses specifically to
11 outcomes from the blinded adjudication process.

12 All of the total joint replacements,
13 including those initially described by
14 investigators as related to osteonecrosis, occurred
15 in two components of the tanezumab development
16 program, highlighted by the gray boxes on the
17 slide, specifically the phase 3 osteoarthritis
18 studies and the phase 2 chronic low back pain
19 studies.

20 There were 373 total joint replacements in
21 the phase 3 osteoarthritis studies and 13 in the
22 chronic low back pain studies, all of which

1 occurred in a non-controlled, long-term study for
2 the latter component.

3 Overall then, 386 total joint replacements
4 were reported in tanezumab studies as of
5 March 2011. Eighty-seven of these 386 total joint
6 replacements, or about 23 percent, were reported to
7 occur in association with an event reported as
8 osteonecrosis by an investigator. And the
9 remaining 299 total joint replacements occurred
10 largely as the result of end-stage osteoarthritis
11 and a few due to joint injury.

12 Although only 50 of the 87 events reported
13 as osteonecrosis had resulted in total joint
14 replacement at the last patient contact, we took
15 the most conservative analytical approach and
16 considered all 87 of these events as total joint
17 replacements. There were 343 patients or 89
18 percent of the overall cohort with a total joint
19 replacement, with documented evidence of
20 osteoarthritis in the affected joint.

21 The event rate of all-cause total joint
22 replacements with placebo, tanezumab monotherapy,

1 tanezumab NSAID combination therapy, and active
2 comparator treatment in the phase 3 osteoarthritis
3 studies are summarized here. Patients receiving
4 tanezumab/NSAID combination therapy were analyzed
5 separately from patients with tanezumab monotherapy
6 due to the differential risk profile of these two
7 treatment regimens in a large, randomized
8 controlled trial, as we described in detail in our
9 briefing document.

10 There were a total of 372 all-cause total
11 joint replacements in the phase 3 osteoarthritis
12 studies and the distribution of total joint
13 replacements across the treatment groups, with the
14 total patient years of exposure shown below each
15 bar.

16 The rate of total joint replacements was
17 similar across placebo, tanezumab monotherapy, and
18 active comparator treatment groups. The rate was
19 markedly elevated in patients treated with a
20 combination of tanezumab and NSAIDs. The rate of
21 all-cause total joint replacements was similar
22 across escalating doses of tanezumab monotherapy,

1 and the event rates were similar to placebo and
2 active comparator treatment.

3 When these same doses were given in
4 combination with NSAIDs, a dose-related increase in
5 the rate of all-cause total joint replacements was
6 observed. And the event rate with tanezumab doses
7 significantly exceeded that of placebo and active
8 comparator treatment by a factor of two- to
9 threefold.

10 There were 13 patients, as I mentioned
11 previously, with an all-cause total joint
12 replacement who were treated with tanezumab alone
13 or non-steroidal agents in the non-controlled,
14 long-term phase 2 chronic low back pain study. The
15 event rates are shown here in the right-hand
16 portion of the panel for tanezumab 10 and
17 20 milligrams combined.

18 The event rates are on the order of four- to
19 fivefold lower than that seen in the phase 3
20 osteoarthritis studies, which are shown in the
21 left-hand panel. Similar to the osteoarthritis
22 studies, however, there is an indication of a

1 treatment difference between tanezumab monotherapy
2 and tanezumab NSAID combination therapy, despite
3 the small number of total joint replacements that
4 were reported.

5 Now, 25 percent of the patients enrolled in
6 this chronic low back pain study had a medical
7 history of osteoarthritis, and definitive or
8 suggestive evidence of osteoarthritis was available
9 for 11 of the 13 patients who underwent total joint
10 replacement.

11 So in summary, the rate of total joint
12 replacements with tanezumab monotherapy were not
13 increased compared to treatment with either placebo
14 or active comparator and no dose-response
15 relationship was observed. The rate of total joint
16 replacements with tanezumab in combination with
17 NSAID therapy was at least twofold greater than
18 placebo, tanezumab monotherapy, or active
19 comparator, and the event rate increased with
20 escalating doses of tanezumab.

21 So recognizing the overlapping radiographic
22 and pathologic features of osteoarthritis and

1 osteonecrosis, we organized a multi-disciplinary,
2 independent adjudication committee with expertise
3 in patients with end-stage osteoarthritis or
4 osteonecrosis, and tasked this committee to review,
5 in a treatment-blinded fashion, all of the
6 available information on adverse events described
7 as osteonecrosis and all other total joint
8 replacements that occurred in the tanezumab
9 clinical program, and to adjudicate these events
10 according to prespecified definitions.

11 The committee reviewed all total joint
12 replacements where a post-baseline radiology image
13 was available within nine months of the surgery.
14 Each member of the committee independently reviewed
15 all source documentation prior to the committee
16 meetings. Each case was reviewed and discussed at
17 committee meetings. And following the case
18 discussion, committee members provided their
19 individual final assessment.

20 The adjudication committee defined four
21 major adjudication outcomes: primary
22 osteonecrosis, worsening osteoarthritis, diagnoses

1 other than worsening osteoarthritis or primary
2 osteonecrosis, and the fourth category of
3 insufficient information to make a determination or
4 a concrete diagnosis.

5 Worsening osteoarthritis was then further
6 subdivided into the following categories: rapidly
7 progressive osteoarthritis, normal progression of
8 osteoarthritis, or insufficient information to make
9 a distinction between those two.

10 Rapidly progressive osteoarthritis was
11 defined as either type 1 or type 2. Type 1 was
12 evidence of loss of joint space with 1 millimeter
13 or greater over approximately a one-year period,
14 and type 2 was evidence of abnormal loss or
15 destruction of bone uncommon for end-stage
16 osteoarthritis.

17 Now, these adjudication criteria were
18 generally similar to those used in the FDA
19 adjudication with two important exceptions. First,
20 the Pfizer adjudication committee adjudicated
21 patients with spontaneous osteonecrosis of the
22 knee, also known as SPONK, to subchondral

1 insufficiency fractures. These events were
2 categorized as osteonecrosis in the FDA
3 adjudication.

4 Secondly, regarding rapidly progressive
5 osteoarthritis, the Pfizer adjudication committee
6 made this determination on occasion on the basis of
7 one x-ray showing bone loss that would be uncommon
8 in a patient with end-stage osteoarthritis. The
9 FDA adjudication criteria for rapidly progressive
10 osteoarthritis required that paired x-rays be
11 available in order to make this determination.

12 These procedural differences resulted in
13 small numerical differences in the adjudication
14 outcomes, but the overall conclusions appear
15 similar.

16 Sufficient information was collected to
17 allow the adjudication committee to examine and
18 adjudicate all of the events reported as
19 osteonecrosis in a little over one-half of the
20 remaining total joint replacements that were
21 reported. Overall, the adjudication committee
22 reviewed the events from 249 of the 386 patients in

1 the tanezumab program with a total joint
2 replacement.

3 Now, we were unable to provide the committee
4 with sufficient information to review and
5 adjudicate the outcome in the remaining 137
6 patients. Nonetheless, given the retrospective
7 nature of the data collection process, a sufficient
8 number of patients were adjudicated to make a great
9 deal of progress in understanding the joint-related
10 safety issue with tanezumab treatment.

11 The adjudication results are summarized over
12 the next several slides, beginning here. Two of
13 the 249 patients, or less than 1 percent, were
14 adjudicated with primary osteonecrosis. The events
15 in both of these patients were identified and
16 reported by investigators as the result of
17 protocol-specified end-of-study x-rays. Neither
18 patient reported pain in the affected joint at the
19 time.

20 One event occurred in the shoulder of a
21 patient treated with tanezumab 10 milligrams, and
22 the second occurred in the hip of a patient treated

1 with 5 milligrams. In both cases, the adjudication
2 committee noted the conditions were longstanding
3 and possibly predating treatment with tanezumab.

4 Based on the adjudication outcomes,
5 therefore, it appears that many of the initial
6 reports of osteonecrosis by investigators were
7 based on the appearance of fragments of necrotic
8 bone due to bone failure commonly seen in end-stage
9 osteoarthritis, and even more so in rapidly
10 progressive osteoarthritis, and are in contrast to
11 the bone changes seen with bone infarction and
12 necrosis, where histological evaluation shows
13 necrotic bone with considerable reparative or
14 reactive changes.

15 The lion's share of the patients, or 200 of
16 249 of the patients adjudicated, or just over
17 80 percent, were adjudicated to the category of
18 worsening osteoarthritis, and this category will be
19 broken down into its subcomponents in the next
20 slide.

21 The committee adjudicated 29 patients or
22 just under 12 percent with conditions other than

1 primary osteonecrosis or worsening osteoarthritis.
2 Patients with subchondral insufficiency fractures
3 accounted for one-third of the patients in this
4 category. End-stage osteoarthritis without
5 evidence of progression was the second more
6 frequent outcome in the category.

7 Next, there were 11 patients which the
8 adjudication committee indicated there was not
9 enough information to definitively assess the
10 event. For a majority of these events, there was
11 either no radiology image available for review or
12 the images were of poor quality.

13 There was unanimous consensus or consensus
14 among the majority of the committee members as to
15 the adjudication outcome in over 97 percent of the
16 cases that were reviewed. There were seven
17 patients with events where the committee did not
18 reach consensus. For these seven patients, none of
19 the adjudication committee members assessed the
20 event as primary osteonecrosis.

21 The events adjudicated to the subcategories
22 of worsening osteoarthritis are broken out on this

1 slide. There were 68 patients, or 27 percent of
2 the patients examined overall, who were adjudicated
3 with rapidly progressive osteoarthritis by the
4 committee. One-half of these patients with rapidly
5 progressive osteoarthritis were reported by
6 investigators initially as an adverse event of
7 osteonecrosis, and the other half were reported as
8 total joint replacements related to worsening
9 osteoarthritis. Over 80 percent of the patients
10 with rapidly progressive osteoarthritis were
11 adjudicated to such on the basis of abnormal loss
12 or destruction of bone, in other words, type 2.

13 Now, in addition to x-rays and other source
14 documentation, this slide summarizes the MRIs and
15 pathology specimens that were available for
16 patients reported with osteonecrosis for review by
17 the adjudication committee. For 70 percent of
18 these patients, either an MRI or pathology specimen
19 was available for review and both were available in
20 approximately 14 percent of the patients.

21 In a similar fashion, MRIs and pathology
22 specimens were available for review by the

1 committee in patients who were adjudicated to a
2 final outcome of rapidly progressive
3 osteoarthritis. For two out of every three
4 patients, either MRI or a pathology specimen was
5 available for review and both were available in
6 approximately 15 percent of patients.

7 So our analysis of the adjudication outcomes
8 are provided on a per-patient basis. In those
9 patients where multiple joints were adjudicated,
10 the worst adjudication outcome was selected for the
11 patient. Other analyses presented today may be on
12 a per-joint basis. And so a side-by-side
13 comparison of the adjudication outcomes on a per-
14 patient basis versus a per-joint basis for the
15 Pfizer adjudication process is shown on this slide.
16 There are no substantial differences between the
17 two approaches.

18 Now, as was the case with the summary of
19 total joint replacements, the analyses of rapidly
20 progressive osteoarthritis that I'm going to
21 present today are by event rates or by incidence
22 rates. These analyses take into account the number

1 of patients exposed to a given treatment and the
2 duration of treatment. These analyses do differ
3 from the analyses by a proportion of adjudicated
4 cases and associated odds ratios that have been
5 provided in the FDA adjudication reports.

6 So there were 67 patients in total
7 participating in the phase 3 osteoarthritis studies
8 with an adjudication outcome of rapidly progressive
9 osteoarthritis and one patient with this outcome in
10 the long-term chronic low back pain study.

11 The rate of rapidly progressive
12 osteoarthritis in the phase 3 studies was greatest
13 in patients receiving tanezumab in combination with
14 NSAID treatment and elevated substantially by over
15 threefold in comparison to tanezumab monotherapy or
16 active comparator treatment. In turn, the rate of
17 rapidly progressive osteoarthritis was also
18 elevated in patients receiving tanezumab
19 monotherapy in comparison to active comparator
20 treatment.

21 Now, to put these event rates into
22 perspective, rapidly progressive osteoarthritis,

1 while higher than active comparator treatment, does
2 not imply that it was a common event necessarily,
3 particularly with tanezumab monotherapy, nor a
4 common reason that patients underwent total joint
5 replacement.

6 The incidence of rapidly progressive
7 osteoarthritis in patients treated with all doses
8 of tanezumab monotherapy combined is 0.4 percent or
9 0.6 percent when accounting for 137 patients with
10 total joint replacements who are not adjudicated.
11 For all-cause total joint replacements, the
12 incidence was five- to sixfold higher at
13 2.7 percent in the phase 3 studies. And in turn,
14 the incidence of each in patients treated with
15 active comparator were 0.1 and 2.2 percent
16 respectively.

17 So there is a definite radiologic
18 distinction in some of the patients treated with
19 tanezumab who progressed to total joint
20 replacement. However, the overall clinical
21 outcome, total joint replacement, is not different.

22 The rate of rapidly progressive

1 osteoarthritis is a function of tanezumab dose
2 administered either as monotherapy or in
3 combination with NSAIDs, as displayed on this
4 slide. The rate of rapidly progressive OA
5 increased as a function of escalating doses of
6 tanezumab, and this was true whether the compound
7 was administered as monotherapy or in combination
8 with NSAIDs. The mean event rate with all doses of
9 tanezumab, in combination with NSAIDs, were
10 elevated, however, when compared to even the
11 highest dose of tanezumab monotherapy.

12 So among many sensitivity analyses, a
13 sensitivity analysis was carried out on the
14 endpoint of rapidly progressive osteoarthritis in
15 order to gauge the impact of missing information
16 that may have led to an underestimation of patients
17 with rapidly progressive osteoarthritis in the
18 tanezumab program. So in this particular analysis,
19 all patients, categorized as either, one,
20 insufficient information to distinguish
21 osteonecrosis from osteoarthritis, two, patients
22 categorized to lack of consensus by the committee,

1 and, three, categorized to insufficient information
2 to distinguish rapid progression of osteoarthritis
3 from normal progression, were added to the
4 adjudicated events of rapidly progressive
5 osteoarthritis.

6 Now, the results of the sensitivity analysis
7 differ from the assessment of adjudicated outcomes
8 of rapidly progressive osteoarthritis alone in that
9 the event rate with tanezumab 2.5 milligrams
10 exceeds active comparator treatment, and a
11 significant difference is now evident between
12 tanezumab 5 milligrams monotherapy and active
13 comparator treatment. However, the sensitivity
14 analysis does not really alter the conclusions that
15 are reached regarding the effects of tanezumab
16 treatment overall.

17 So patients participating in the controlled
18 phase 3 osteoarthritis studies were randomized to
19 tanezumab NSAID combination treatment. And the
20 effect of administering tanezumab in combination
21 with NSAIDs on the event rate of rapidly
22 progressive osteoarthritis was demonstrated in

1 randomized controlled studies alone, was
2 demonstrated in the non-controlled, long-term
3 studies alone, and in the combination of these two
4 groups of studies, as I just presented.

5 Now, per protocol in the non-controlled
6 long-term phase 3 osteoarthritis studies, patients
7 were permitted to receive NSAID treatment with
8 tanezumab if warranted, based on the clinical
9 judgment of the investigator. And in these
10 long-term OA studies, 1498 patients used NSAIDs
11 concomitantly with tanezumab and 1322 patients did
12 not.

13 The event rate of rapidly progressive
14 osteoarthritis in NSAID users was 23 events per
15 1,000 patient years and significantly greater than
16 the event rate in non-NSAID users of 6 events per
17 1,000 patient years.

18 In the analysis of the FDA adjudication
19 outcomes, all of these patients would have been
20 included in the tanezumab monotherapy treatment
21 group. The risk of rapidly progressive
22 osteoarthritis appears to be related to the

1 duration of therapy, as shown on this slide, by
2 duration of NSAID use in 30-day intervals. The
3 analysis shows a pattern of increased risk of
4 rapidly progressive osteoarthritis when NSAIDs are
5 used concomitantly with tanezumab for periods of
6 90 days or greater.

7 Given the nature of the adjudication
8 outcomes, I think it would be helpful to spend a
9 bit of time reviewing some of what is known about
10 rapidly progressive osteoarthritis. Rapidly
11 progressive osteoarthritis is well-recognized in
12 the orthopedic, radiology, and pathology literature
13 by various names, some of which are listed here.

14 The condition was first described by
15 Forestier in a doctoral dissertation in 1957, and
16 there have been over 100 publications on this
17 condition since 1970.

18 Rapidly progressive osteoarthritis is
19 typically considered to be a naturally occurring
20 form of osteoarthritis that occurs predominantly in
21 the hip and less commonly in the knee and shoulder.
22 Up to one-sixth of patients with hip osteoarthritis

1 can be affected by this condition. A key
2 characteristic of the condition is severe,
3 progressive joint destruction with focal joint
4 space narrowing and extensive subchondral loss in
5 the femoral head, the acetabulum, or both.

6 Now, Peter Bullough and colleagues from the
7 Hospital of Special Surgery in New York have
8 published extensively on rapidly progressive
9 osteoarthritis and the relationship of this
10 condition to subchondral insufficiency fractures.

11 In one of their publications, which is cited
12 here, there is an excellent example of the
13 radiologic features of rapidly progressive
14 osteoarthritis. In this paper, they show a series
15 of x-rays from a 57-year-old woman who had a
16 14-month history of bilateral hip pain prior to the
17 time of the first radiograph.

18 The image labeled "A" on the left
19 demonstrates slight joint space narrowing and cyst
20 formation in the lateral margin of the acetabulum
21 in both hips, with more severe narrowing in the
22 right hip. The changes were considered to be

1 consistent with early degenerative joint disease.

2 After just five months, the patient's
3 clinical symptoms worsened and her joint space
4 narrowing had progressed. As shown in the middle
5 image, the right hip joint space had almost
6 disappeared to less than 1 millimeter, and on the
7 left side, the joint space had decreased to
8 approximately 3 millimeters.

9 The patient's pain became increasingly worse
10 and after an additional five months, the image on
11 the right shows the joint spaces in both hips had
12 totally disappeared. And both femoral heads had
13 undergone massive collapse. The patient
14 subsequently underwent bilateral total hip
15 arthroplasty.

16 So based on the 10-month radiograph from
17 this patient, this patient would meet the
18 definition of rapidly progressive osteoarthritis
19 type 2, and, in fact, an extreme example of such.
20 This patient -- and there are many other papers
21 with similar findings -- clearly showed that the
22 degree of bone loss or joint destruction in some of

1 the patients with osteoarthritis who participated
2 in the tanezumab program is not an unprecedented
3 observation. The radiologic characteristics are
4 not the central issue.

5 The issue is the higher rate of occurrence
6 of these events in patients receiving tanezumab and
7 even more so in patients who receive tanezumab in
8 combination with non-steroidal drugs. Whether
9 tanezumab or other anti-NGF inhibitors act to
10 further accelerate the ongoing process of rapidly
11 progressive osteoarthritis, or act to initiate
12 rapid progression in susceptible patients, or both,
13 is unclear at the present time.

14 This series of x-ray images is from a
15 63-year-old woman enrolled in a tanezumab clinical
16 study. She reported having generalized OA for five
17 years prior to enrolling in the study. Her index
18 joint was the right hip, which is shown in the
19 image on the left, and was graded by the
20 investigator as KL grade 4 prior to the patient
21 enrolling in the study.

22 The image in the middle panel was taken two

1 weeks prior to the patient enrolling in the study
2 and shows worsened OA relative to the image
3 obtained approximately four months earlier. As you
4 can see, increased bone loss, and based on this
5 radiograph, the adjudication committee adjudicated
6 the patient as having rapidly progressive
7 osteoarthritis prior to study entry.

8 Now, the patient was enrolled in the study
9 and randomized to tanezumab 5 milligrams treatment.
10 At week 32, in other words, eight months, the
11 patient reported an increase in right hip pain,
12 which progressed, and she discontinued from the
13 study one month later. The x-ray in the right
14 panel shows collapse of the right femoral head,
15 consistent with type 2 rapidly progressive
16 osteoarthritis.

17 The patient went on to have total hip
18 replacement. Pathology slides showed bone erosion
19 with granulation tissue and extensive detritus in
20 the synovial membrane with bone fragments, findings
21 consistent with rapidly progressive osteoarthritis.

22 So in addition to the patient described

1 here, the adjudication committee concluded that
2 eight additional patients with an adjudication
3 outcome of rapidly progressive osteoarthritis was
4 pre-existing, that is, was evident prior to the
5 patient entering a phase 3 osteoarthritis study and
6 receiving study medication. The events were
7 equally split between the knee and hip joints.
8 Four of the events were categorized as type 1, and
9 five were categorized as type 2, including the case
10 shown here.

11 This slide outlines some of the important
12 clinical characteristics of tanezumab-treated
13 patients with rapidly progressive osteoarthritis.
14 Evidence was available to establish that
15 osteoarthritis was present in the affected joint
16 prior to treatment in 61 patients or 9 out of every
17 10 patients with this condition.

18 There was no available information to make
19 this determination in six patients, and the
20 remaining one patient in this cohort had minimal to
21 no osteoarthritis in the affected joint. However,
22 the patient experienced a subchondral insufficiency

1 fracture that was evident prior to the
2 determination of rapidly progressive
3 osteoarthritis.

4 I want to take a moment also here to draw
5 attention to the fact that the one case of rapidly
6 progressive osteoarthritis in the knee of a patient
7 participating in the chronic low back pain study
8 occurred in a 76-year-old woman with severe lateral
9 osteoarthritis in the same knee prior to study
10 entry and osteoarthritis of multiple joints since
11 2003.

12 A majority of the patients had rapidly
13 progressive osteoarthritis of the hip, and the
14 proportion well exceeded the 23 percent of patients
15 in the overall study population, with hip as the
16 index joint.

17 Finally, as shown in the graph off to the
18 right, the proportion of patients with rapidly
19 progressive osteoarthritis in joints that were
20 Kellgren-Lawrence grade 2 was well below the
21 proportion of patients with index joints KL grade 2
22 in the overall study population.

1 The following clinical observations may have
2 some importance in elucidating the mechanisms
3 involved in the development of rapidly progressive
4 osteoarthritis with NGF inhibition. First, no
5 patients with this condition, or any other patient
6 in the tanezumab program, for that matter, have
7 been identified with loss of protective sensation.
8 Secondly, the neurologic characteristics of
9 patients with rapidly progressive osteoarthritis
10 also did not differ from the overall treated
11 population.

12 Second, a direct link of greater pain relief
13 to rapidly progressive osteoarthritis could not be
14 established. However, the findings do not exclude
15 that pain relief may contribute or accelerate
16 further damage in a susceptible joint such as one
17 with greater subchondral bone pathology, and/or
18 susceptibility to a subchondral insufficiency
19 fracture, or atrophic osteoarthritis. There was
20 also no evidence that greater pain relief accounted
21 for the greater risk of rapidly progressive
22 osteoarthritis with tanezumab NSAID combination

1 therapy.

2 So in summary, adjudication confirmed two
3 patients with primary osteonecrosis. Rapidly
4 progressive osteoarthritis was the adjudication
5 outcome in a little over one quarter of the
6 patients adjudicated. This outcome was observed,
7 for the most part, in patients with osteoarthritis
8 and joints with moderate to severe osteoarthritis.

9 There was a dose-related increase in the
10 rate of rapidly progressive osteoarthritis with
11 tanezumab monotherapy over active comparator. And
12 the rate was further increased by threefold or more
13 when tanezumab was administered in combination with
14 NSAIDs. Co-administration of NSAIDs for up to
15 90 days with tanezumab treatment did not appear to
16 elevate the risk of rapidly progressive
17 osteoarthritis and, finally, some of these events
18 were adjudicated as pre-existing by the committee.

19 So the rationale for the risk minimization
20 procedures that I'm going to address next are an
21 outgrowth of the observations of the analyses made
22 on rapidly progressive osteoarthritis as described

1 in my presentation today. In other words, they are
2 evidence based.

3 The rationale for the risk -- so the
4 rationale's listed here. The risk of rapidly
5 progressive osteoarthritis increases with chronic,
6 concomitant NSAID use. Secondly, in
7 osteoarthritis, tanezumab 10 milligrams did not
8 provide additional benefit over 5 milligrams.
9 Third, preliminary review of the data suggests that
10 most patients who respond to tanezumab do so after
11 1 to t2 doses. And fourth, review of the baseline
12 radiographs show that some patients have rapidly
13 progressive osteoarthritis at study entry. And
14 this was the evidence used to define the risk
15 management measures going forward.

16 So here we show the risk minimization
17 measures again in the left-hand column of this
18 table. The right-hand column displays the number
19 of tanezumab-treated patients in the phase 3
20 osteoarthritis studies with rapidly progressive
21 osteoarthritis who would have been impacted by the
22 risk minimization measure and the cumulative

1 percent reduction in the number of patients with
2 rapidly progressive osteoarthritis.

3 As can be seen, excluding chronic
4 concomitant NSAID use with anti-NGF therapy is by
5 far the most effective measure to reduce the risk
6 of rapidly progressive osteoarthritis.

7 Overall, these four risk minimization
8 measures would have reduced the number of patients
9 with rapidly progressive osteoarthritis by
10 95 percent if they had been in place prior to the
11 tanezumab phase 3 osteoarthritis program.

12 Another analysis to illustrate the
13 effectiveness of the risk minimization measures are
14 shown here. In the left panel, the incidence of
15 rapidly progressive osteoarthritis observed in the
16 phase 3 osteoarthritis studies are shown for all
17 tanezumab-treated patients combined, all patients
18 receiving tanezumab monotherapy, all patients
19 receiving tanezumab NSAID combination therapy, and
20 finally all patients treated with active
21 comparator, moving from left to right.

22 The number needed to harm, as compared to

1 active comparator treatment, are shown above each
2 tanezumab treatment bar. The NNT, the number
3 needed to treat, versus active comparator treatment
4 to achieve a WOMAC pain reduction of 50 to
5 90 percent, is on the order of 6 to 15.

6 The results displayed in the right panel are
7 those that would have been evident in the phase 3
8 program if the risk minimization measures had been
9 implemented prior to the start of the program. The
10 incidence of rapidly progressive osteoarthritis
11 with tanezumab 2.5-milligram alone, 5-milligram
12 alone, or these two doses combined, are similar to
13 active comparator treatment. And the number needed
14 to harm are increased substantially from those
15 determined from the observed results shown on the
16 left.

17 Now, in a similar fashion, the effectiveness
18 of the risk minimization measures can be
19 demonstrated using a composite endpoint with the
20 adjudication outcomes of rapidly progressive
21 osteoarthritis, primary osteonecrosis, and
22 subchondral insufficiency fractures combined. This

1 endpoint would closely agree with the events as
2 categorized by the adjudication process, carried
3 out on behalf of the FDA.

4 So again, moving to other categories and
5 other factors, our path forward in terms of the
6 sponsors, further measures to protect safety to
7 further characterize the risk and to safely conduct
8 clinical trials in the future will be described in
9 the presentations that follow.

10 So in conclusion, I'm going to end where I
11 began. Tanezumab relieves pain and improves
12 function across a variety of chronic pain
13 conditions. And where it has been evaluated, it is
14 superior to active comparator treatment. Tanezumab
15 monotherapy does not elevate the risk of all-cause
16 total joint replacements. This is in contrast to
17 the observations when tanezumab is administered in
18 combination with NSAIDs.

19 Adjudication of the total joint replacements
20 show tanezumab does not elevate the risk of
21 osteonecrosis, but rather is associated with a
22 dose-related increase in rapidly progressive

1 osteoarthritis, which is further increased by
2 threefold or more when administered with NSAIDs.

3 Finally, risk minimization measures,
4 identified as an outgrowth of the analyses we have
5 conducted, should reduce the risk of rapidly
6 progressive osteoarthritis in future clinical
7 studies. Thank you for your attention.

8 **Industry Presentation - David Upmalis**

9 DR. UPMALIS: Good morning. I'm David
10 Upmalis from Janssen. We appreciate the
11 opportunity to work with this committee to ensure
12 that promising new therapies for pain can be safely
13 studied in patients who have not found adequate
14 relief from medications that are currently
15 available.

16 Our findings are supportive of what was seen
17 with tanezumab. Janssen has demonstrated promising
18 results in models of nociceptive and neuropathic
19 pain. Similar to the tanezumab findings, increased
20 rates of RPOA have been detected in patients with a
21 prior history of osteoarthritis, in combination
22 with NSAIDs, and primarily in our add-on study.

1 Implementation of appropriate risk
2 minimization will enable the resumption of clinical
3 trials to establish the safety and utility of
4 anti-NGF compounds in the treatment of chronic pain
5 in populations with significant unmet need.

6 It's important to keep in mind that these
7 agents show promise in both osteoarthritis and
8 non-osteoarthritis pain states, and separate paths
9 may apply in consideration of resuming trials.

10 Data on fulranumab arise from two phase 1
11 studies, as well as seven phase 2 trials with up to
12 two years of observation. At the time of the
13 clinical hold, over 1200 subjects had been treated
14 in fulranumab studies.

15 Except for the interstitial cystitis and the
16 monotherapy OA trial, all studies had extension
17 phases that contributed to total exposure achieved.
18 The phase 2 studies generated over 900 patient
19 years of observation of fulranumab-exposed subjects
20 at doses ranging from 1 to 10 milligrams every four
21 weeks.

22 To begin, this presentation will focus on

1 the add-on OA study because most of the joint
2 replacements arose here. Following this, the
3 presentation will touch on the encouraging results
4 seen in the diabetic painful neuropathy study.

5 The add-on OA study recruited subjects with
6 moderate to severe pain that was not adequately
7 controlled by current therapy. Study medication
8 was added to stable doses of the analgesic
9 medications the subjects were taking at baseline,
10 mostly NSAIDs.

11 Subjects were randomized to placebo, 1 or
12 3 milligrams of fulranumab every four weeks, or 3,
13 6, or 10 milligrams of fulranumab administered
14 every eight weeks. Following an initial 12-week
15 primary observation period, subjects were enrolled
16 in a 92-week double-blind extension.

17 All subjects were entered into a 26-week
18 follow-up after the last dose, regardless of where
19 in the study this occurred, in order to determine
20 if anti-drug antibody responses arose. This is in
21 contrast to clinical trials often conducted
22 studying NSAIDs or opiates, where follow-up ends

1 shortly after the last dose of study medication.

2 During this 26-week period, subjects were
3 seen regularly for blood draws, and safety data
4 were obtained, including information about any
5 completed or planned joint replacements.

6 It's important to note that approximately
7 80 percent of subjects were taking NSAIDs at
8 baseline and continued them into this study. This
9 study, then, primarily represents a comparison of
10 fulranumab plus NSAIDs, to placebo plus NSAIDs, and
11 would correspond to the Pfizer analyses of
12 tanezumab plus NSAIDs and NSAIDs alone.

13 A pre-defined efficacy analysis on the
14 primary endpoint, done at 12 weeks, showed that the
15 maximum analgesic effect was observed in subjects
16 treated with an intermediate dose of fulranumab,
17 3 milligrams every four weeks. Two other treatment
18 groups, the 6- and 10-milligram every-eight-week
19 groups, were significantly better than placebo as
20 well. In separate analyses, significant results
21 were also seen for both WOMAC pain and WOMAC
22 function measures. The add-on trial demonstrates

1 promising results of improvement in pain and
2 function and favorable tolerability with low
3 discontinuation rates.

4 There have also been promising results in a
5 study of fulranumab in the relief of pain of
6 diabetic peripheral neuropathy. The DPN study was
7 a dose-ranging study to evaluate efficacy of
8 fulranumab in subjects with diabetic, neuropathic
9 pain. After the initial double-blind efficacy
10 period, there was an open-label safety extension.

11 As with the OA trial, this trial also
12 utilized an add-on design, with subjects allowed to
13 continue their DPN pain medications into this
14 trial, with some dosage restrictions such that all
15 subjects using other therapies were on approved
16 doses of those therapies.

17 Doses of study medication, placebo, 1, 3, or
18 10 milligrams of fulranumab, were administered
19 every four weeks. The primary observation period
20 was 12 weeks. As with the OA study, there was a
21 26-week follow-up period after discontinuation of
22 therapy.

1 The primary objective of this study was to
2 demonstrate a dose-response relationship in pain
3 relief at week 12. Despite early termination of
4 enrollment due to the clinical hold, the study met
5 the primary endpoint and a linear dose response was
6 demonstrated.

7 The solid line shows the linear plot of the
8 dose response. This is encouraging, given that
9 only 77 of the originally planned-for 200 subjects
10 were enrolled. Of particular interest is the
11 finding that the 10-milligram, every 4-week group
12 separated from placebo with statistical
13 significance in a pairwise comparison. The
14 tolerability of fulranumab in this study generally
15 reflected what had been seen previously.
16 Importantly, there were no joint replacements in
17 this study.

18 The fulranumab efficacy and tolerability
19 data in both OA and DPN reflect the promise of the
20 anti-NGF class of compounds. The results are
21 consistent with those observed in the tanezumab
22 clinical program. When we look at joint

1 replacements, our communications with the FDA have
2 focused on events that may represent osteonecrosis
3 and/or rapidly progressive osteoarthritis. We were
4 advised by the FDA that regardless of the
5 underlying condition, the event of interest
6 resulted in joint replacement.

7 Accordingly, our investigations primarily
8 focused on cases that underwent joint replacement.
9 A review of the incidence of joint replacement
10 presents a complex picture. The percentage of
11 joint replacements by study and by treatment groups
12 supports the findings of Pfizer's studies. The OA
13 add-on study demonstrated the highest percentage of
14 joint replacement with some excess in the
15 fulranumab-treated subjects compared to placebo.

16 As I mentioned, approximately 80 percent of
17 subjects were taking NSAIDs at baseline and
18 continued them into the study. And it's noteworthy
19 that this finding is similar to the finding in the
20 tanezumab data, that tanezumab plus NSAID appears
21 to have an elevated risk of joint replacement over
22 tanezumab or placebo alone.

1 The low back pain study, with 311 patient
2 years of observation in the fulranumab group and a
3 similar extent of use of non-steroidal
4 anti-inflammatory drugs as the add-on OA study, did
5 not reveal near the percentage of joint
6 replacements compared to the OA add-on study and
7 does not demonstrate any significant excess of
8 joint replacements compared to placebo.

9 We became aware of the work that the
10 tanezumab team had undertaken in evaluating their
11 joint cases, and in order to further examine our
12 cases, we too convened an adjudication panel. The
13 committee was multi-disciplinary and blinded to
14 treatment. It was independent of the tanezumab
15 adjudication committee. At the outset, the
16 committee agreed to definitions of normal OA
17 progression, rapidly progressive osteoarthritis,
18 osteonecrosis, insufficient information, or not
19 applicable, and subsequently adjudicated the cases
20 presented to them.

21 In total, 102 joint replacements and
22 7 joint-related adverse events that had not

1 undergone total joint replacement, but were
2 considered AEs suspicious of significant joint
3 events, were considered for adjudication. Of the
4 joints adjudicated, 72 were adjudicated to normal
5 progression of osteoarthritis. No joints were
6 adjudicated as osteonecrosis. A total of 18 joint
7 replacement cases were classified as RPOA by the
8 adjudication committee.

9 Sixteen of the 18 joints came from the
10 add-on osteoarthritis study, one from the
11 post-herpetic neuralgia study, and one from the low
12 back pain study. All of the cases were randomized
13 to fulranumab.

14 All of the subjects had a history of
15 osteoarthritis in the affected joint, though one of
16 these subjects did not have documented
17 osteoarthritis by radiograph at baseline. All were
18 taking NSAIDs when they entered their respective
19 trials.

20 I would note there seems to have been a
21 misinterpretation of the data that resulted in the
22 Columbia group, in certain analyses, assigning

1 these cases as anti-NGF without NSAID. This may be
2 a misclassification.

3 There were three treatment groups in the PAI
4 2004 of the add-on study, those subjects who did
5 not have a joint replacement, those adjudicated to
6 normal OA with joint replacement, and then those
7 subjects, in this case 15 subjects in this trial
8 that were adjudicated to rapidly progressive
9 osteoarthritis.

10 Note that all subjects with RPOA were on
11 NSAIDs at the start of the study compared to 83
12 percent of the subjects in the non-joint
13 replacement group. No cases of RPOA were operated
14 on until at least after 5 doses of study drug were
15 administered and the median number of doses was 11.

16 Given the small numbers in our data, we
17 could not assess a dose response. The wide
18 confidence intervals around the percentage of RPOA
19 in each treatment group overlap considerably.
20 Summarizing the adjudication, then, osteonecrosis
21 as defined by our expert panel was not found.
22 There was a finding that RPOA was associated with

1 administration of fulranumab.

2 Most cases were found in the OA add-on
3 study. In our data, all cases reported a prior
4 history of symptoms of osteoarthritis in the
5 affected joint and were taking NSAIDs. Given the
6 few cases identified, a dose-response relationship
7 could not be evaluated.

8 The data from the fulranumab studies support
9 the findings from the tanezumab presentation and
10 point to a path forward to resume clinical trials
11 for the anti-NGF class. The incidence of joint
12 replacement varies considerably among trials. An
13 increase in joint replacement in fulranumab-treated
14 subjects compared to placebo was only evident in
15 our add-on study where there was extensive use of
16 NSAIDs, similar to the data presented by tanezumab
17 where the incidence was higher in the tanezumab
18 plus NSAIDs group compared to tanezumab or placebo
19 alone.

20 The incidence of RPOA varies similarly and
21 in fact the data provide little evidence that there
22 is a hazard in subjects who do not have

1 osteoarthritis. Recognizing these factors, the
2 objectives of future studies will vary depending
3 upon the populations studied.

4 Here are some thoughts about
5 non-osteoarthritis studies. If one were to design
6 a study of an anti-NGF agent for a non-OA pain
7 state, for example diabetic peripheral neuropathy,
8 it's evident that a likelihood of RPOA or even
9 joint replacement is not an outcome of great
10 interest or great likelihood to occur. Rather, we
11 would focus on determining the appropriate doses to
12 develop and define the minimum effective dose of
13 the study medication, which may vary from
14 osteoarthritis.

15 Recognizing that the study population may
16 have subjects with concurrent osteoarthritis, it is
17 important to consider the implication of the doses
18 to be investigated, as some doses might be higher
19 than what is proposed to be studied in the OA
20 population. These subjects warrant particular
21 attention and safeguards can be built in for such
22 subjects. There may be other disease-specific

1 concerns that should also be addressed.

2 Returning to osteoarthritis, a review of the
3 tanezumab data show that in treatment groups of
4 tanezumab without NSAIDs, the incidence of total
5 joint replacement was similar to placebo and to
6 active comparator, even though cases of RPOA were
7 seen in the 5- and 10-milligram treatment groups.
8 The incidence of joint replacements were only
9 increased in the tanezumab plus NSAID groups.

10 An important question to ask is what is the
11 safety outcome of interest in future anti-NGF
12 studies? Is it RPOA? Is it total joint
13 replacement? Is it both?

14 Looking forward, then, and given the
15 relatively short time it takes to demonstrate
16 efficacy compared to the time to develop joint
17 symptoms, these studies can characterize the
18 efficacy of doses to be studied. It would be most
19 important, though, to confirm that the elimination
20 of NSAIDs reduce the incidence of RPOA. This needs
21 to be evaluated in the context of total joint
22 replacements. Is there an acceptable risk of RPOA

1 if total joint replacements are not increased or
2 even reduced? This question is important, and we
3 welcome the committee's thoughts on this.

4 Assuming that some residual events of
5 interest do occur, these studies will enable the
6 collection of prospective data that may provide
7 further insight into these events. We need to know
8 what other factors might contribute to an
9 individual's hazard for RPOA.

10 In summary, fulranumab data support the
11 tanezumab findings that efficacy is attractive in
12 both nociceptive and neuropathic pain and that a
13 safety signal of the use of anti-NGF compounds in
14 association with NSAIDs in the OA population
15 results in cases of RPOA.

16 The elimination of NSAIDs should
17 significantly decrease this hazard. There does not
18 appear to be a similar risk in non-OA populations.
19 In resumption of clinical trials, strategies can be
20 developed to address these issues facing the
21 compounds in both OA and non-OA pain. Thank you
22 for your kind attention.

Industry Presentation - Ned Braunstein

DR. BRAUNSTEIN: Good morning. I am Ned Braunstein. I'm the head of regulatory affairs at Regeneron Pharmaceuticals. Regeneron has been studying neurotrophic factors and their biology since 1989, when we were involved in the initial cloning of the nerve growth-related factors BDNF, neurotrophin 3, and neurotrophin 4/5.

Over the past few years, Regeneron has been developing, in collaboration with Sanofi Pharmaceuticals, RGN475. RGN475 is a fully human IgG-4 monoclonal antibody that specifically binds to human, monkey, mouse, and rat nerve growth factor and blocks nerve growth factor signaling through its TrkA and P75 receptors.

We should caution that, as with any class of drugs, not all members of that class need have the same exact effects and exact same side effects. In this particular case, antibodies to nerve growth factor may also bind to closely related members of the neurotrophin family, such as neurotrophin 3, which plays a major role in regulating

1 proprioception. Even transient low-affinity
2 binding could have effects. We carefully selected
3 and validated RGN475 to ensure that it has no
4 detectable binding to nor blocks signaling by other
5 neurotrophins, notably NT-3, NT-4/5, or BDNF.

6 We appreciate the opportunity to be here
7 today, to participate in this meeting, and to
8 contribute to the further development of a
9 promising new class of drugs to address the unmet
10 needs of patients with pain. And we're also here
11 today to learn more about the data that prompted
12 the FDA's concerns so that we can refine our
13 proposed path forward.

14 Our position at Regeneron and Sanofi is that
15 the current data provide evidence for the efficacy
16 of anti-NGF therapy and that there is a possible
17 role for anti-NGF therapy in pain conditions where
18 there is unmet need, that is, where there are no
19 adequate alternatives. However, there are
20 concerning safety signals. Thus, the current data
21 do not support anti-NGF therapy as a treatment for
22 all patients with osteoarthritis or other pain.

1 The observed safety signals need to be understood
2 much better before treatment should be extended to
3 this broad group of patients.

4 A description of the RGN475 development
5 program is included in the briefing book in the
6 addendum. This presentation will summarize our
7 phase 2 efficacy and safety data, our joint-related
8 safety data, and some preliminary non-clinical data
9 from a murine model of osteoarthritis. I will then
10 present Regeneron and Sanofi's conclusions. And
11 finally, I will provide a common proposal from all
12 the sponsors on a proposed path forward for removal
13 of the clinical hold.

14 At the time we were placed on clinical hold,
15 we were in the midst of proof-of-concept studies
16 and were still evaluating different pain conditions
17 to determine those in which RGN475 might provide
18 efficacy. We had completed it first in human study
19 and exploratory studies in osteoarthritis of the
20 knee and sciatic pain.

21 The sciatic pain study did not show
22 efficacy, so I will focus on the osteoarthritis

1 study. We had terminated because of difficulty in
2 enrolling patients, studies in patients with
3 thermal-injury pain, chronic pancreatitis pain, and
4 vertebral fracture pain. Data from all of these
5 studies are provided in the briefing book. Our
6 safety database contains 509 subjects, of whom 357
7 were exposed to active drug.

8 The osteoarthritis study was a randomized,
9 double-blind placebo-controlled study in
10 approximately 200 subjects. Details about study
11 design are in the briefing book. The key efficacy
12 variable shown here was a change from baseline in
13 daily walking knee pain. Patients had a rapid
14 response to the first infusion of RGN475 and a dose
15 response was evident.

16 A separation between the doses was not seen
17 after the second infusion, and analgesic effects of
18 all doses were seen through week 16. Other
19 endpoints, such as WOMAC score and patient global
20 impression of change, were consistent with these
21 data.

22 This slide provides the common

1 musculoskeletal and nervous system adverse events
2 in the osteoarthritis study. These adverse events
3 were more frequent in patients treated with RGN475
4 than placebo and several showed a dose response.
5 However, almost all were mild to moderate in
6 severity and discontinuations were only observed in
7 the highest-dose group. And while these data are
8 limited, we did not see any association between
9 these events and subsequent joint events or
10 fractures.

11 We first became aware that there was a
12 joint-related safety signal in the other sponsors'
13 databases in July 2010. At that time, we had
14 completed the osteoarthritis and sciatic pain
15 studies, and the others had been stopped due to
16 poor enrollment. Our safety database contained two
17 patients who had total joint replacement during
18 clinical studies. Then in December of 2010, we
19 were placed on clinical hold together with Janssen
20 Pharmaceuticals and before we had an opportunity to
21 initiate further studies.

22 At the request of the FDA, we initiated a

1 retrospection collection of data. We sent letters
2 to our investigator sites and to the IRBs and asked
3 them to contact patients and identify cases of
4 total joint replacement or exacerbation of pain.
5 Through this process, we identified 10 additional
6 patients who had 12 total joint replacements. Case
7 information, x-rays, and pathology were obtained if
8 possible, but in many cases, the information was
9 incomplete.

10 So there were a total of 14 total joint
11 replacements identified in our studies. These were
12 all hip and knee replacements. Twelve of the cases
13 occurred in 10 patients who had been treated with
14 RGN475. The other two were in patients treated
15 with placebo. All of the patients had a history of
16 osteoarthritis. In addition, two patients had
17 lower-limb fractures, both of which were traumatic.

18 Because of the retrospective and incomplete
19 nature of the data, we too convened an adjudication
20 panel consisting of a rheumatologist, bone
21 radiologist, and bone pathologist. They conducted
22 a blinded, independent review, and then discussed

1 at a meeting their assessments as to whether each
2 total joint replacement case was consistent with
3 normal osteoarthritis progression, or, if not, if
4 the cause was osteonecrosis, rapidly progressive
5 osteoarthritis, or something else, and to explain
6 why. They then provided their final written
7 assessments.

8 Twelve of the cases were considered normal
9 progression of osteoarthritis. There were no
10 patients adjudicated to have osteonecrosis.

11 However, there was one patient with a subchondral
12 fracture, who was thought to possibly have rapidly
13 progressive osteoarthritis. Details about this
14 patient are in your briefing book.

15 Clearly, the database of patients developed
16 by Regeneron and Sanofi prior to the clinical hold
17 is too small to support or refute the idea that
18 there was a risk of unanticipated joint damage
19 during the use of RGN475.

20 As is standard in drug development, we and
21 the other sponsors conducted routine toxicology
22 studies that included evaluations of bone

1 vasculature and nerves in normal animals. In
2 addition, Regeneron conducted studies to understand
3 if there was a biologic basis to explain the
4 clinical observations that the other sponsors had
5 shared with us. Specifically, we explored a murine
6 model of osteoarthritis as a tool to investigate
7 the effects of RGN475 and of NSAIDs on bone,
8 cartilage, joint innervation, and vasculature.

9 The data I am about to summarize are from
10 two small studies involving 3 to 7 animals per
11 treatment group. And some of the findings have not
12 yet been reproduced. Moreover, the studies did not
13 produce the expected cartilage loss from
14 surgically-induced destabilization of the medial
15 meniscus, and there was a lot of variability in the
16 data and lack of consistency between related
17 treatment groups for certain measures. However, at
18 the request of the FDA, we are summarizing these
19 preliminary results today.

20 We conducted two experiments in a mouse
21 model of osteoarthritis in which the medial
22 meniscotibial ligament is surgically transected,

1 leading to medial meniscus instability in the
2 subsequent development of an osteoarthritis-like
3 condition. The first study evaluated the effects
4 of RGN475 monotherapy, and the second study
5 evaluated the effects of RGN475 with or without a
6 non-steroidal anti-inflammatory drug.

7 The first experiment found no significant
8 effect of RGN475 on any measures tested. Those
9 data are in your briefing book. In the second
10 experiment, we evaluated the effects of treatment
11 with RGN475 combined with indomethacin. Whereas in
12 the first experiment, drug treatment was initiated
13 the day after surgery, in the second experiment,
14 drug treatment was not initiated for 16 weeks.

15 This second study was implemented as a pilot
16 study after learning some of the tanezumab clinical
17 data, and it therefore did not include all of the
18 necessary control groups. Moreover, there are
19 additional endpoints still being analyzed.
20 Therefore, we ask that the committee view the
21 results as preliminary data and recognize the need
22 for additional experiments.

1 There were no significant effects of drug
2 treatment on vascular density or general bone
3 pathology and no significant effects of RGN475
4 alone on cartilage markers. However, there were
5 suggestive but highly variable decreases in
6 cartilage markers in DMM, in the destabilized
7 medial meniscus-operated animals that received
8 combination therapy of RGN475 with indomethacin.

9 In addition, serum tartrate-resistant acid
10 phosphatase or TRAcP 5b levels, which are used as a
11 measure of osteoclast activity, were significantly
12 elevated in all animals receiving combination
13 therapy, regardless of their surgical manipulation.
14 We feel that these preliminary non-clinical study
15 data do not allow us to make any meaningful
16 interpretations or conclusions, but are worth
17 repeating and following up.

18 It is our conclusions from the data we have
19 seen today that there is evidence for efficacy with
20 all of the drugs in the anti-NGF class. There is
21 also a signal that needs to be presumed or ruled
22 out for each agent, and this must be done

1 prospectively in the intended patient populations
2 with the intended dose, and must compare efficacy
3 and safety in these same prospectively designed
4 experiments in order to determine the true overall
5 benefit versus risk.

6 It is also important to acknowledge that
7 while it may be possible to limit risk by a lower
8 dose of one agent, it may also be possible that the
9 risks may be different amongst the agents in the
10 class. Therefore, our immediate next steps in
11 osteoarthritis would be to explore benefit risk in
12 patients who might have most to gain from this new
13 therapy, that is, clinically meaningful superior
14 efficacy to NSAIDs in poor NSAID responders and
15 clinically meaningful efficacy over baseline in
16 patients intolerant to NSAIDs.

17 If this committee were to have concerns that
18 the risk profile might still not be appropriate in
19 such populations, we would focus on clinical
20 benefit of shorter-term therapy in late-stage
21 patients awaiting total joint replacement.

22 Another key question we would explore is

1 whether subcutaneous administration in intervals
2 shorter than monthly will result in improved safety
3 by minimizing Cmax, and we would continue to
4 explore our non-clinical studies using larger
5 cohorts of mice to see if we could reproduce any of
6 the preliminary results; and in particular, whether
7 a biomarker could be defined that might identify
8 patients at risk. Based on these data, we will
9 then discuss a confirmatory efficacy and safety
10 program with the FDA.

11 So I will now change hats and speak on
12 behalf of all the sponsors. Based on our preview
13 of each other's analyses that you have seen today,
14 each of the sponsors proposed a path forward in
15 their briefing book. And despite the fact that
16 each sponsor was at a different stage of
17 development, these proposals were well aligned.
18 Therefore, I am able to present to you a common
19 sponsors' proposed path forward. We are also
20 interested in learning more about the analyses
21 performed by Drs. Bathon and Colburn and the
22 recommendations of the FDA and this committee.

1 This common proposal is predicated on being
2 able to demonstrate a clinically significant
3 benefit over existing options and an acceptable
4 safety profile, thus establishing a positive
5 benefit risk in patients with unmet need.

6 The removal of the clinical hold is based
7 on, first, informed consent of patients and
8 communication of risks to investigators and IRBs,
9 which we will do in consultation with the FDA.
10 Although this might be obvious, it is worth
11 emphasizing.

12 We propose to expand screening in baseline
13 evaluations to include standardized x-rays of major
14 joints in both osteoarthritis and non-
15 osteoarthritis studies, and a standardized pain
16 questionnaire.

17 seek to minimize the risks of rapidly
18 progressive osteoarthritis by adopting the safety
19 exclusions that you have heard about in the
20 previous presentations.

21 We would all exclude the chronic use of
22 NSAIDs. As it would be impractical and probably

1 impossible to preclude their use, our clinical
2 trials would limit NSAID use to treatment for
3 intercurrent events. And based on this approach,
4 the safety data will reflect what we anticipate to
5 be real-world use.

6 All the sponsors have proposed to limit the
7 dose of anti-NGF therapy in osteoarthritis studies.
8 And in non-osteoarthritis studies, where higher
9 doses of anti-NGF may be used, we would exclude
10 patients with advanced osteoarthritis. Lastly, all
11 of the sponsors would exclude patients with a
12 history of rapidly progressive osteoarthritis from
13 all of our studies.

14 To ensure that all events of interest are
15 identified, all studies will include the use of the
16 standardized pain questionnaire at specified
17 intervals, and we will conduct an end-of-study
18 safety follow-up for all patients, including those
19 who discontinue drug.

20 Osteoarthritis studies will include annual
21 radiographs of the hips and knees with centralized
22 reading and an additional post-study follow-up of

1 joint safety, which will include assessments of
2 functional status and history of joint-related
3 events. For those patients who undergo total joint
4 replacement, we will collect surgical and
5 three-month post-operative outcomes.

6 To standardize the evaluation of joint-
7 specific events, we will expand the collection of
8 information beyond the typical case and operative
9 reports to include original radiographs and, where
10 possible, pathology slides or the tissue block.
11 The collected information will be evaluated by each
12 sponsor's centralized adjudication committee.

13 Finally, to protect patient safety, all
14 patients with new or worsening joint pain will
15 undergo thorough evaluation, and drug will be
16 discontinued or surveillance increased in patients
17 with new findings. An independent data monitoring
18 committee for each sponsor will monitor the safety
19 data.

20 I would now like to introduce Dr. Nathaniel
21 Katz, who will discuss the risk-benefit potential
22 of NGF inhibitors in various patient populations.

Industry Presentation - Nathaniel Katz

DR. KATZ: Good morning, ladies and gentlemen of the committee. Let me first acknowledge that you've been sitting there for a long time, listening to these presentations and you've absorbed a lot of data. So the end is near. This presentation is quick, and there's not any new data that you really need to remember, so you can relax a little bit.

By way of brief introduction, I'm a neurologist and a pain management physician from Boston. I spent the first half of what is now getting to be a 20-year career taking care of patients with acute and chronic pain, including cancer pain as the head of the pain program at the Dana-Farber Cancer Institute. And for the last dozen or so years, I've been focusing my attention on trying to develop better treatments for pain than the ones that we have now.

By way of a quick conflict of interest disclosure, I do run a small consulting and clinical research firm in Boston, and we work with

1 most sponsors who are developing analgesics. And
2 I've worked with two out of the three sponsors at
3 today's meeting. However, I have no financial
4 interest in any of those companies or any financial
5 interest in the outcome of this or any other FDA
6 advisory committee meeting.

7 We're here today to deliberate on a very
8 specific issue. Should the clinical hold on the
9 anti-NGF antibodies be lifted? And if so, how can
10 we study these medications in a way that protect
11 our patients?

12 I'm here because I believe that your
13 deliberations may have implications that reach
14 beyond the issue of these specific medications, and
15 they affect the future of better development of
16 better treatments for pain, to which I have devoted
17 a great deal of time and effort.

18 Let's begin by reflecting for a moment on
19 who it is exactly that we're trying to help.
20 You've seen some epidemiologic data already from
21 Dr. Schnitzer. I personally like this particular
22 survey, which was commissioned in the late 1990s, a

1 survey of 500,000 U.S. households that set very
2 strict criteria for who qualified as having chronic
3 pain, depending upon both their duration as well as
4 their severity.

5 You don't have to be an epidemiologist to
6 figure out that our communities are filled with
7 people, friends, family, neighbors with highly
8 impactful chronic pain conditions of various types.
9 And lest you believe that arthritis pain is
10 currently well treated, the data to the contrary
11 indicate that the majority of patients with
12 arthritis, which is mostly osteoarthritis, rate
13 their pain as severe or very severe, despite access
14 to all of our available treatments.

15 What are these treatments that people are
16 currently using for their pain? There are about
17 180 million prescriptions for opioids per year in
18 the United States. Don't forget that there are
19 only about 200 million adults in this country. And
20 there are over 4 million long-term opioid users, of
21 whom about one-third indicate that they use opioids
22 for osteoarthritis.

1 There are over 14 million people in the
2 United States using non-steroidal anti-inflammatory
3 drugs on an ongoing basis, with about 90 million
4 prescriptions per year, not counting over-the-
5 counter use.

6 There are about 63 million
7 prescriptions -- I don't know how well you can see
8 that. There are about 63 million prescriptions per
9 year for what we used to call adjunctive
10 analgesics, which include things like gabapentin or
11 reuptake inhibitors. And finally, over 400 million
12 dose packs of over-the-counter analgesics, which is
13 acetaminophen and non-steroidal anti-inflammatory
14 drugs, primarily sold per year. The take-home
15 message is that people with pain will take
16 medications for relief of their suffering in large
17 numbers, despite known or suspected risks.

18 What are those risks? Although opioids have
19 been used for thousands of years, useful estimates
20 of their actual risks have only emerged very
21 recently. The risk of overdose among
22 patients -- and that's people that we've prescribed

1 opioids to -- is almost 2 percent per year, higher
2 for patients with recent opioid prescriptions or
3 with certain risk factors.

4 About 5 percent of patients prescribed
5 hydrocodone will develop an abuse or an addiction
6 problem within a year. On a national level, almost
7 2 million Americans meet criteria now for
8 full-blown addiction to prescription opioids, which
9 is almost 1 percent of our adult population. These
10 risks are substantial and have been known about for
11 a long time. Yet, opioids have also been described
12 as God's own medicine, and I don't think any of us
13 would want to live in a world where we had no
14 access to these medications.

15 What about the NSAIDs? Although there is
16 some debate about the exact number, there are
17 thousands of deaths per year due to GI bleeding
18 alone, with estimates that 1 to 2 percent of
19 regular NSAID users will develop serious GI events
20 at some point, of whom about 80 percent have no
21 warning. NSAIDs also cause substantial increases
22 in cardiovascular morbidity, including congestive

1 heart failure and myocardial infarction.

2 Despite these risks, all of us use NSAIDs.
3 Most of you probably have Advil or Motrin in your
4 bag right now, as I do. The point is that in the
5 calculus of human suffering, people like you and
6 me, when we are in pain, will decide that the risks
7 are worth it to escape from whatever it is that's
8 tormenting us.

9 You'd think that we would have developed
10 something better by now. My personal career
11 mirrors this string of failures that Dr. Schnitzer
12 enumerated earlier. I don't think it's an
13 exaggeration to say that billions of dollars have
14 been spent both by the U.S. federal government and
15 the pharmaceutical industry in search of a strong,
16 safe pain reliever.

17 This is a partial list of new molecular
18 entities that I myself have studied in patients and
19 you will notice that none of them are on the
20 market. Virtually all new chemical entities
21 designed to hit new targets have failed to show
22 meaningful analgesia in patients with pain until

1 the anti-NGF antibodies came along that we're
2 discussing today.

3 You've seen this before. It's from your
4 briefing package. To see a drug that provides
5 superior pain relief, not only to placebo but to
6 our current standards, is more or less unheard of.
7 Usually, you're lucky if you can beat placebo. And
8 even drugs that we accept as effective often can't
9 beat placebo in clinical trials. Furthermore, to
10 see superiority in terms of physical function,
11 which for most of our patients is how pain affects
12 their quality of life and productivity, is
13 something I myself have not seen in another class
14 of analgesics to date.

15 But what about the risks of these drugs that
16 we've heard so much about today? First, let's
17 remember that these drugs are still in development.
18 It's unrealistic to expect that the risks of any
19 new class of drugs will be fully characterized in
20 the developmental stage.

21 Having said that, joint replacements and
22 rapidly progressive osteoarthritis are serious

1 complications that need to be fully characterized.
2 It's possible that the risks that we will be
3 discussing in detail today will end up to be less
4 of a problem than they appear now. It's also
5 possible they'll continue to be a problem or that
6 new risks will emerge.

7 What I did on this slide is to pull together
8 summary information on rates of serious adverse
9 events from various parts of your briefing package,
10 focusing on tanezumab monotherapy as an example, as
11 proposed in the risk mitigation plan.

12 In doing so, I'm not trying to convince you
13 about how these rates were quantified, nor whether
14 all the relevant adverse events are presented here,
15 or whether these rates are good or bad. You
16 probably have your own opinion about that and, if
17 not, you'll hopefully have one by the end of the
18 day.

19 What I am trying to suggest to you is that
20 you should consider these events in context and in
21 their totality. Don't just look at isolated
22 adverse events; look at them all together. And

1 don't forget about your active comparators, which
2 are widely used but far from harmless.

3 Given this stage of development, none of us
4 can say right now how the risk-benefit profile of
5 the anti-NGF antibodies will ultimately compare to
6 our existing, not-so-ideal alternatives. We won't
7 know unless we complete the studies. But I do know
8 that if we don't have at least a little courage to
9 proceed and study new treatments, we will continue
10 to relegate our patients with chronic pain, the
11 very people we are trying here to protect, to their
12 fate, which is far from acceptable.

13 What are the alternatives to proceeding with
14 cautious development? One option would be to study
15 only risk-free medications. If that's our policy
16 and position, we may as well turn off the lights
17 and go home because, unfortunately for this
18 foreseeable future, all pain treatments will have
19 risks.

20 Or maybe we should only accept risks for
21 diseases that we take seriously like cancer, or
22 multiple sclerosis, or HIV disease. I firmly

1 believe that the members of this committee
2 understand the seriousness of such a highly
3 prevalent and frequently disabling condition as
4 osteoarthritis and related conditions, and would
5 not accept such a position.

6 Or maybe we should just accept the status
7 quo, where less than half of our patients get
8 meaningful pain relief from our currently available
9 treatments and thousands die per year from
10 complications of those treatments. Or we can just
11 wait for something better to come along.

12 We are here today because of a deeply rooted
13 respect for Hippocrates's first principle, primum
14 non nocere -- and I did look up how to pronounce
15 that -- first, do no harm. We all respect this as
16 our first ethical obligation to our patients;
17 otherwise, we would not be here.

18 But what's our second obligation? The
19 second pillar of our professional credo is
20 beneficence, the ethical obligation to help our
21 patients. Just not harming is easy. All we have
22 to do is stay home, leave our patients to suffer,

1 and we can't be accused of harming anybody.
2 However, in order to help, we do need to study new
3 treatments that at least have the potential to be
4 safer or more effective than what we have now.

5 In summary, I'm here to offer the following
6 thoughts to this committee. First, leaving the
7 patients in their current condition is no kind of
8 protection. Second, in order to fulfill our
9 obligation, to attempt to provide some kind of
10 beneficence, we do need to study treatments that at
11 least offer the hope of better safety and efficacy
12 than what we have now, despite some level of risk
13 commensurate with the risk level that these
14 patients are already experiencing.

15 I don't know whether the anti-NGF antibodies
16 will ultimately have the type of risk-benefit
17 profile that will merit approval by the FDA, but I
18 do know that if we don't do some type of studies,
19 we won't find out. In our well-intentioned zeal to
20 do no harm, let's not forget who we're protecting
21 and what their needs actually are.

22 Now, it's up to you in your deliberations to

1 figure out how we can best move forward to help our
2 patients and to protect them.

3 DR. BUCKLEY: Thank you very much.

4 Before we move on to clarifying questions, I
5 wanted to take a minute to let Dr. Curtis
6 Rosebraugh introduce himself. He's been here since
7 the beginning of the meeting, but just for the
8 record.

9 DR. ROSEBRAUGH: Hi. I'm Curtis Rosebraugh,
10 director, Office of Drug Evaluation II.

11 **Clarifying Questions to the Industry**

12 DR. BUCKLEY: Thank you.

13 For the next 15 minutes, we're going to
14 proceed to clarifying questions, not discussion,
15 but just what information you need about the data
16 or clarifications of programs or suggestions of the
17 sponsor.

18 If you let us know going around the room,
19 we'll try to take you in order as people raise
20 hands. And again, if you would identify yourself
21 on the microphone and turn off the microphone when
22 you're done speaking.

1 We'll start with Dr. Suarez.

2 DR. SUAREZ-ALMAZOR: Yes. I had a few
3 questions for Dr. Verburg with respect to his
4 presentation. And I'll just ask the questions, but
5 it's about four or five questions.

6 Can I ask them all? Or are you asking me to
7 pick and choose?

8 DR. BUCKLEY: Why don't we start with the
9 first one or two, and then we'll see.

10 DR. SUAREZ-ALMAZOR: Okay. The first one
11 is, you presented in one of your slides that there
12 were 17 OA studies, but the data that you showed
13 for joint replacement was just a minority of those
14 studies. So I was wondering if there was any data
15 for the rest, or perhaps I didn't understand what
16 you meant.

17 Also, the length of observation for the
18 studies that you presented, I was not sure if it
19 was just during the duration of the trial or there
20 was longer follow-up for those patients. And
21 related to that as well, you said that one-third
22 were not adjudicated, so I was wondering -- it's

1 approximately about 130, I think, of the total were
2 not adjudicated to any of the groups. And I'd like
3 to know what group they belonged to, the ones that
4 you were not able to diagnose.

5 DR. VERBURG: That was one long question.

6 DR. SUAREZ-ALMAZOR: I know. I thought I
7 would put three into one.

8 DR. VERBURG: She put more questions in the
9 one question.

10 Well, I'll try to peel them back. And if I
11 forget to answer them as I go along, just correct
12 me.

13 I think your first question related to how
14 many of these osteoarthritis studies were included
15 in the cohort of studies that we evaluated for
16 total joint replacements. The answer is quite
17 straightforward. I showed you a slide earlier on
18 in the morning that we had done 17 studies in
19 osteoarthritis. Thirteen of those studies were one
20 in the phase 3 development program. There were, in
21 fact, no total joint replacements in the phase 2
22 osteoarthritis program, which consisted of three

1 studies. We discarded those studies. We didn't
2 include them in our analysis cohort. So that left
3 us with 13 studies.

4 Of the 13 studies, 11 of them were included
5 in the analysis cohort that I showed today. The
6 reason for that was that the two studies we did not
7 include enrolled a total of 2 patients and 22
8 patients. And we didn't have a chance and an
9 opportunity to identify those slides or actually
10 unblind those trials until we had worked out
11 through the others.

12 There was one total joint replacement in
13 there and that's why you see a difference between
14 some of my slides of 373 and 372. Bottom line, 11
15 studies were evaluated, and that's the data that
16 you've seen this morning.

17 Okay? So hopefully that answers the study
18 question.

19 What was the next question?

20 DR. SUAREZ-ALMAZOR: Length of follow-up for
21 the ones that were not adjudicated.

22 DR. VERBURG: Yes. So typically, in our

1 program, we will follow patients four months after
2 the last dose. And so that would be sort of a
3 standard procedure for each clinical trial. In the
4 particular case of the clinical hold, however, it's
5 somewhat of an unusual circumstance when all of
6 your clinical trials stop at once. It's not really
7 something that you predict. And so there is some
8 observation period beyond four months in the last
9 dose, but it's really just going out to about six
10 months, and then it falls off quite quickly
11 thereafter.

12 Another?

13 DR. SUAREZ-ALMAZOR: Yes. And the third,
14 that were not adjudicated.

15 DR. VERBURG: The treatment distribution?
16 Oh, I'm sorry; for the non-adjudicated patients.
17 Yes. Let me take you through that.

18 Why don't we just show this quickly. How
19 about B-97?

20 So here, you see the profiles of the
21 adjudicated patients. Again, the cohort was 249.
22 In the non-adjudicated patients, the cohort was

1 137. And here, you see the treatment distribution
2 for the non-adjudicated cases along the right-hand
3 column. So they correspond to a little under
4 5 percent at placebo. And you can generally
5 see -- I think the take-away there is they're
6 generally similar. So the treatment distributions
7 were similar between non-adjudicated and
8 adjudicated patients.

9 DR. BUCKLEY: Dr. Morrato?

10 DR. MORRATO: Thank you. This is Elaine
11 Morrato. I also had a question for Dr. Verburg.
12 It relates to slide A-52 when you're talking risk
13 minimization. And I first want to say, I really
14 appreciated the way that you approached the
15 description in trying to anticipate how it might
16 translate into real world. So my questions are
17 kind of thinking in light of that translation.

18 So I want to make sure I understand the N of
19 66 patients.

20 DR. VERBURG: Sure.

21 DR. MORRATO: Are these adjudicated? And
22 recognizing that it came from 249, I think, cases

1 that went into adjudication, did you look at that
2 as a denominator, recognizing that the real world
3 is going to be messy, people aren't going to be
4 appropriately categorizing to start? And then do
5 you have a similar slide for the chronic low back
6 pain in which we know that 5 milligrams was not
7 shown as effective? So I would imagine patients
8 would be on 10 milligrams.

9 DR. VERBURG: I think there were three
10 questions in that question.

11 DR. MORRATO: No, it was two.

12 DR. VERBURG: Let's go to slide A-52. I
13 believe this is the slide that you were referring
14 to.

15 DR. MORRATO: Correct.

16 DR. VERBURG: And you're asking me, where do
17 those 66 patients come from? The 66 patients are
18 66 of the 68 patients that had an adjudication
19 outcome of rapidly progressive OA. They subtract
20 out the 1 patient that had bilateral rapidly
21 progressive osteoarthritis, who was treated with
22 naproxen, and it also excludes the patient that was

1 in the chronic low back pain program.

2 So that's how we get the denominator of 66.
3 And then we take you through the number of patients
4 by the various risk minimization strategies.

5 I think your second question related to,
6 have we tried other things to evaluate the
7 uncertainty. No?

8 DR. MORRATO: Yes.

9 DR. VERBURG: So in a sense, how effective
10 would this be with other assumptions. We've done a
11 couple things. One you saw this morning is to take
12 a wider composite endpoint, which includes a lot
13 more patients of the 249. Right? Because we're
14 including ON patients. We're including 10 patients
15 with subchondral insufficiency fracture, and
16 brought them into the numerator, and did the same
17 process of walking them down through these various
18 steps. You saw the outcome was pretty favorable.

19 What we've also done is put back in all of
20 the events that I showed you in the sensitivity
21 analysis this morning. They all got put back into
22 this. And again, we carried the numerator down

1 through a greater amount.

2 We've also done it with total joint
3 replacements, so all 386. It's not quite as
4 effective with all-cause total joint replacements,
5 primarily because, as you recall, the dose-response
6 relationship for all-cause total joint replacements
7 wasn't like it was in rapidly progressive
8 osteoarthritis.

9 DR. MORRATO: So to summarize, did all of
10 those scenarios achieve over 90 percent risk
11 minimization, or what was the range?

12 DR. VERBURG: Not all achieved over 90, but
13 except for total joint replacements overall, which
14 was in the high 80s, they did.

15 DR. MORRATO: Thank you.

16 DR. BUCKLEY: Dr. Neogi?

17 DR. NEOGI: I have a question for all the
18 sponsors. Given the short length of follow-up, we
19 don't have very much information about how these
20 replaced joints are functioning. I wanted to know,
21 for those that had existing joint replacements,
22 were there any safety concerns there in terms of

1 revision, loosening, et cetera, that might have
2 been unexpected?

3 DR. VERBURG: I'll start, and I won't be
4 that helpful, I'm afraid. Let me just make sure I
5 clarify your question. You're speaking
6 specifically of those patients that had an outcome
7 of rapidly progressive osteoarthritis, had the
8 joint procedure, and are you asking, how did they
9 do? No?

10 DR. NEOGI: So I guess two questions. If
11 you do have that long-term follow-up information
12 for those, yes. But also, for those that had an
13 existing joint replacement, who entered the study?

14 DR. VERBURG: Yes. I think that the number
15 of revisions that we saw overall was vanishingly
16 small. I'm not even sure I can remember one case.
17 I will tell you that about on the order of
18 3 percent of patients came into the osteoarthritis
19 program with a total joint replacement. I can't
20 recall off the top of my head that anyone had an
21 issue with revision. Sorry I didn't get your
22 question earlier.

1 DR. BRAUNSTEIN: Yes. This is Ned
2 Braunstein from Regeneron. So we have very little
3 data. We had no cases of revisions or any problems
4 with patients who had prior joint replacements. We
5 had short-term follow-up in the two patients who
6 had joint replacements during the study, and there
7 were no problems with either of those. But again,
8 we have very limited data to answer that question.

9 One of the things that the sponsors have all
10 proposed, which is an important part of the
11 proposed path forward, is that we will
12 prospectively gather information on the functional
13 outcomes of all total joint replacement cases,
14 approximately we figured three months after
15 surgery. That way we'll have a good handle on
16 whether or not there are problems.

17 DR. BUCKLEY: Dr. Gabriel?

18 DR. GABRIEL: Sherine Gabriel. Three
19 questions, the first two for Dr. Verburg and the
20 last one, really, for everybody. The first
21 question has to do with your efficacy data. I
22 notice that in many of your analyses, you use the

1 approach of last observation carried forward.

2 Can you share or remind us of the missing
3 data in the treated and non-treated arms? What
4 were the proportions of missing data and dropouts?

5 I'll give you my second question. You also
6 shared the 87 reports of osteonecrosis from the
7 individual investigators. How many individuals
8 does that represent? I mean, it's not 87 reports
9 of 87 individuals, or how many investigators does
10 that represent, that made those reports?

11 Then I can just ask my third question and
12 wait. My third question really has to do with
13 definitions, so definitions of rapidly progressive
14 OA and definitions of osteonecrosis. What
15 definitions were used in the various studies?

16 So I'll stop there.

17 DR. VERBURG: So first thing, I want to just
18 cycle back and maybe correct a statement you made,
19 maybe not. All of the analyses that I showed in
20 the tables comparing tanezumab doses to placebo or
21 to active were based on baseline carried
22 forward -- or baseline observation carried forward,

1 not last observation carried forward.

2 So anyone that discontinued the trial had
3 their baseline score imputed back into the result.
4 So that's typically considered to be a very
5 conservative analysis because anybody who responds,
6 at least initially, and then discontinues the
7 treatment for some reason, they are out.

8 Now, as to the proportions of who
9 discontinued or what was the rates of
10 discontinuation, I mean, the rates of
11 discontinuation with tanezumab are not like one
12 sees with CNS active drugs. It's not three or four
13 times higher than it is background. It's very
14 close to placebo and very close to active
15 comparator treatment.

16 So I think my general comment is there
17 really isn't too much difference in differential
18 dropout on the efficacy results.

19 Now, I'm sorry. You had a couple others.

20 DR. BUCKLEY: I think maybe for lack of
21 time, we'll try to move to a couple more questions.
22 We only have about a few minutes left.

1 I'll start with Dr. Neaton.

2 DR. NEATON: Actually, I have a question for
3 Dr. Verburg as well. I'm over here. Could you put
4 up slide A-21?

5 DR. VERBURG: Sure. A-21?

6 DR. NEATON: While you're putting that up,
7 just to note, baseline observation carried forward
8 doesn't have to be conservative. In fact, it's
9 very anti-conservative in terms of standard errors.
10 But we'll come back to that.

11 I'd just like some explanation of this
12 slide, which is kind of fundamental to your
13 conclusions, as well as the one by dose. And so
14 you've combined here all the studies, the phase 3
15 studies. And what I'm concerned about here is that
16 one big study, study 125, 1025, it didn't have a
17 placebo arm. Right? So you've got comparisons
18 here that are not protected by randomization.

19 DR. VERBURG: True

20 DR. NEATON: So can you give us some data
21 that are protected by randomization? Because you
22 had a variety of comparator arms in these different

1 studies, some which are suitable for comparing
2 dose, some which are suitable for comparing mono
3 versus NSAID combination therapy, and some which
4 are suitable for comparisons against placebo. And
5 I think, potentially, we may be misled by just
6 throwing them all together like this.

7 DR. VERBURG: Let me show you a slide where
8 all of the data is in a similar format or at least
9 for controlled trials.

10 DR. NEATON: And, obviously, this is true
11 for A-23, the dose comparison slide, too. In
12 general, you did a nice job of going through the
13 different studies for efficacy, taking into account
14 what the different comparators were. And I think
15 we need to see the same thing for the safety.

16 DR. VERBURG: Yes. I can't find the exact
17 slide that I was looking for, but I think B-19 will
18 do. Yes. Please show that slide.

19 So this is a very similar analysis, but by
20 dose. And it shows we're in the controlled trials
21 now, so per randomized treatment. Okay? And
22 again, study 1025, which we outline in our briefing

1 document, is a large component of this, but about a
2 third.

3 DR. NEATON: But this comparison is not
4 protected by randomization, either.

5 DR. VERBURG: Well, I mean, you can only
6 collect the control trial dataset and provide it as
7 a group sum.

8 DR. NEATON: But you can -- for us to get an
9 understanding of whether tanezumab monotherapy is
10 worse than placebo --

11 DR. VERBURG: Worse than placebo alone?

12 DR. NEATON: Right. Or even worse than the
13 comparator, we need to kind of see the data in
14 which those were the randomizations.

15 DR. VERBURG: Can I see B-25 on the preview?

16 Okay. We can start here for active, so
17 let's start with the B-25. This was the data that
18 we showed in the briefing document. And meanwhile,
19 my colleagues can maybe find a comparison of
20 control trials versus placebo.

21 So this is the 1025 trial, as per randomized
22 treatment. All right?

1 DR. NEATON: Right.

2 DR. VERBURG: And this is the observation,
3 Dr. Neaton. And it really drove a lot of what we
4 did subsequently. Right? We based it on this
5 observation. We felt this was randomized, it was
6 controlled, and we would build the story up from
7 there.

8 Now, can we find some evidence to show that
9 in a control trial setting, as randomized, that the
10 joint replacements are similar with tanezumab
11 treatment to monotherapy?

12 DR. NEATON: I mean, if we want to
13 take -- we can come back to it.

14 DR. VERBURG: Can I see M-56B. Let me see
15 that on the preview.

16 Okay. Why don't we put this up? This is a
17 little bit different approach, but this is the
18 meta-analysis approach for the placebo-controlled
19 trials. Please show the slide 560.

20 Sorry that's so small, but you see here,
21 along the left, all studies that had a placebo
22 treatment group. And then you see a comparison of

1 tanezumab 5 milligrams to placebo, either by
2 eliminating a study with zero events or correcting
3 for studies with zero events, and you see the
4 relative odds ratios there.

5 As you go down, I'll just direct your
6 attention down to the bottom, that the odds ratio
7 of tanezumab 5 milligrams therapy, in any event, to
8 placebo here was less than 1.

9 DR. BUCKLEY: Our time for questions is up
10 for now, but we're going to have an opportunity to
11 address some of these questions when we get to the
12 discussion part this afternoon. So we'll keep the
13 list of people who are interested in asking more
14 questions.

15 We knew today was going to be challenging.
16 We're going to take just a 10-minute break and meet
17 back here by 10:45.

18 (Whereupon, a recess was taken.)

19 DR. BAUTISTA: Please begin to take your
20 seats. The meeting will start very soon.

21 DR. BUCKLEY: We will now proceed with the
22 FDA presentation.

FDA Presentation - Janet Maynard

DR. MAYNARD: Good morning. My name is Janet Maynard, and I'm a rheumatologist and medical officer with the FDA in the Division of Pulmonary, Allergy, and Rheumatology Products. It is my pleasure to welcome you to Washington. I would like to thank the members of the Arthritis Advisory Committee for being here today to share your expertise.

Here is an outline of the FDA's presentations. Our goal is to perform a risk-benefit assessment of the anti-nerve growth factor agents. In order to perform this assessment, I will first provide a brief overview of the natural history of osteoarthritis. This will be followed by a review of safety concerns by Dr. Pokrovnichka. She will also briefly review the efficacy of these agents. Lastly, Drs. Colburn and Bathon will review serious joint-related adverse events.

These presentations should provide a framework for evaluating the risk-benefit profile of the anti-nerve growth factor agents.

1 A key issue in our discussion is an
2 understanding of the natural history of OA and how
3 often and to what degree rapid joint destruction
4 might be observed in patients with OA. Thus, I
5 will provide background on the natural history of
6 OA with an emphasis on the subset of patients with
7 OA who have more rapid clinical decline.

8 I will compare OA with the clinical,
9 radiographic and pathologic features of other
10 causes of joint destruction. I will refer to these
11 causes of joint destruction as rapidly destructive
12 arthropathies.

13 OA is a potential cause of joint
14 destruction. Most commonly, patients with OA have
15 a slowly progressive disease course, as represented
16 by the solid line. However, this is a
17 heterogeneous disease in which there is a spectrum
18 of disease progression, as represented by the
19 dashed and dotted lines.

20 In this talk, I will examine characteristics
21 of rapid decliners with OA. The literature
22 suggests that involvement in a clinical trial is

1 associated with more rapid decline. However, even
2 in a large clinical trial of patients with knee OA,
3 less than 15 percent of patients experienced
4 disease progression after two years.

5 I will contrast this spectrum of disease
6 progression in OA with the characteristics of other
7 potential forms of rapidly destructive
8 arthropathies, such as osteonecrosis and Charcot
9 neuroarthropathy. Also, I will contrast the
10 characteristics of patients with OA with the rapid
11 and unexpected joint destruction seen in patients
12 with the phenomenon described by the sponsors as
13 rapidly progressive osteoarthritis in the anti-
14 nerve growth factor trial experience. I will begin
15 my talk by reviewing OA.

16 OA is a complex disease affecting the whole
17 joint. It is characterized by a slowly progressive
18 joint degeneration in which there is a loss of
19 cartilage matrix, followed by ineffective repair.
20 OA is the most common joint disorder in the world.
21 In 1990, an estimated 12 percent of the United
22 States population or about 21 million people had a

1 physician diagnosis of OA.

2 Clearly, OA is associated with aging. In
3 addition, female gender, obesity, and previous
4 trauma are recognized risk factors for OA. OA is a
5 heterogeneous disease. It can be accompanied by
6 pain. However, the correlation between
7 radiographic evidence of OA and pain is weak. OA
8 can affect any joint, but the weight-bearing joints
9 are generally more symptomatic when they are
10 affected by OA. Certain joints such as the
11 shoulder are less likely than the knee or hip to
12 develop end-stage OA requiring joint replacement.
13 A previous study suggested that there is a pattern
14 to the evolution of OA, with OA in one weight-
15 bearing joint influencing the progression of OA in
16 other joints.

17 Radiographically, OA is generally
18 characterized by hypertrophic changes such as
19 osteophytes. In addition, joint space narrowing
20 and bony sclerosis can be seen. Pathologic
21 specimens demonstrate primarily degenerative
22 changes. Although it is not a predominant feature

1 of the disease, osteonecrosis can also be present.
2 A previous evaluation observed secondary
3 osteonecrosis in 11.7 percent of femoral heads
4 removed surgically because of OA.

5 The natural history of OA is difficult to
6 describe due to the heterogeneity of the disease
7 itself and the heterogeneity in how disease
8 progression is monitored. It is important to note
9 that there is no standard definition of disease
10 progression. Most studies use radiographic or
11 clinical criteria to monitor disease progression.
12 However, there is significant variability in the
13 definitions of disease progression.

14 Total joint replacement is frequently used
15 as a surrogate marker for end-stage OA. However,
16 joint replacement is generally an elective
17 procedure and numerous factors, including
18 ethnicity, gender, and psychosocial considerations,
19 influence an individual's decision to undergo total
20 joint replacement. Thus, there is no gold standard
21 for total joint failure.

22 Several radiographic grading scales have

1 been developed to define radiographic disease
2 severity and to monitor OA progression. The most
3 commonly used grading scale was developed by
4 Kellgren and Lawrence. The KL system divides OA
5 into five grades ranging from zero to 4. Key
6 radiographic features include the presence of
7 osteophytes, joint space narrowing, and subchondral
8 sclerosis. This table gives an overview of the
9 features used to grade OA according to the KL
10 system. A score of 2 or greater has traditionally
11 been thought to represent OA.

12 In OA, there's a spectrum of disease
13 progression. This spectrum was seen in the knee OA
14 structural arthritis or KOSTAR study. The KOSTAR
15 study evaluated the effect of risedronate on OA
16 progression in patients who had knee OA.
17 Risedronate did not impact structural progression.
18 Thus, this study provides a large amount of
19 information regarding radiographic disease
20 progression in OA.

21 In this study of 2,483 patients, progressors
22 were defined as individuals with a decrease in

1 joint space of at least .6 millimeters after
2 24 months. The histogram on the right side of the
3 screen displays the percent of patients by the mean
4 joint space with change in millimeters over
5 24 months. Eighty-seven percent of patients did
6 not have significant radiographic changes in joint
7 space over 24 months. There is a small subgroup of
8 patients who did have radiographic disease
9 progression. However, the maximal joint space loss
10 appeared to be less than 2.5 millimeters in
11 24 months.

12 OA has also been noted to be a slowly
13 progressive disease in the community. The
14 Framingham study evaluated the natural history of
15 knee OA in 869 subjects. Over a mean of eight
16 years of follow-up, the rates of new radiographic
17 and symptomatic OA were higher in women than men.

18 Incident radiographic knee OA was defined as
19 the development of a modified Kellgren-Lawrence
20 score of at least 2 during follow-up.

21 Approximately 2 percent of women developed incident
22 radiographic knee OA. Only half of these

1 participants developed clinical symptoms in
2 addition to radiographic findings. In terms of
3 baseline disease progression in one year, only 4
4 percent of women with OA at baseline had disease
5 progression, defined as an increase in Kellgren-
6 Lawrence score by at least one grade.

7 Thus, disease progression from the
8 Framingham cohort suggests a slow evolution of OA
9 over time, with most subjects remaining stable.
10 This slow evolution is demonstrated on radiographs
11 from the American College of Rheumatology Image
12 Bank. This composite image of four knee
13 radiographs demonstrates slowly progressive joint
14 damage over 19 years in a woman with OA. The
15 initial film on the left demonstrates sclerosis of
16 the medial tibial plateau. Subsequent films show
17 development of large medial osteophytes,
18 subchondral cysts, and joint space loss. After 19
19 years, there is lateral subluxation of the tibia
20 relative to the femur and collapse of the medial
21 tibial plateau. The image on the far right
22 displays images of severe radiographic OA.

1 Patients with severe OA may consider joint
2 replacement surgery.

3 This table displays the proportion of
4 subjects undergoing total knee replacement in the
5 osteoarthritis initiative or OAI study. The OAI
6 study is a multi-center prospective observational
7 study. The progression sub-cohort of the OAI study
8 was similar to the OA patients in the anti-nerve
9 growth factor clinical trials. Patients in the
10 progression cohort had clinical symptoms and
11 radiographic signs of OA at baseline and were
12 followed for disease progression. In contrast,
13 patients in the incident sub-cohort of the OAI
14 study did not have symptomatic OA at baseline, but
15 had risk factors for the development of knee OA.

16 A study by Riddle, et al evaluated the
17 incidence of total knee replacements in the
18 progression cohort in patients who had two-year
19 follow-up data available at the time of the
20 analysis. 3.7 percent of subjects with baseline
21 symptomatic knee OA underwent a total knee
22 replacement during two years of follow-up. For the

1 subgroup of patients with symptomatic end-stage OA
2 at baseline, the proportion undergoing the
3 arthroplasty after two years was only 9.7 percent.
4 A follow-up analysis was performed on the
5 progression and incidence cohorts after three
6 years. Of subjects with baseline end-stage knee
7 OA, only 12 percent underwent total knee
8 replacement after three years.

9 Thus, data from a U.S. community-based
10 cohort suggests that greater than 85 percent of
11 patients with end-stage knee OA will not undergo
12 knee replacement surgery during three years of
13 follow-up. These data are consistent with the
14 results of the knee OA structural arthritis study
15 and with analyses from other clinical trials of
16 potentially disease-modifying OA drugs.

17 We have reviewed the natural history of OA,
18 and I have highlighted data indicating there is a
19 spectrum of disease progression, with a small
20 subset of patients having a more rapid disease
21 progression. Data suggests that patients enrolled
22 in a clinical trial or considering surgery tend to

1 have more rapid disease progression.

2 The key issue for you to consider today is
3 whether the rapid joint destruction seen in the
4 clinical trials of anti-nerve growth factor agents
5 is unusual in patients with OA, even after
6 recognition that more rapid disease progression can
7 occur in OA.

8 I will now review types of rapidly
9 destructive arthropathies that are relevant to the
10 anti-nerve growth factor development programs.

11 Rapidly destructive arthropathy is a
12 descriptive term that can be applied to a variety
13 of processes that lead to rapid and unexpected
14 joint destruction. There is a long differential of
15 potential causes of rapid joint destruction and
16 these causes can have overlapping features.

17 Frequently, pathologic specimens reveal
18 necrosis and degeneration. Thus, patients may not
19 fit into a specific diagnostic category.
20 Furthermore, categorizing just based on diagnostic
21 classification overlooks an important aspect of
22 this category of arthropathies, which is the poor

1 outcome for the patient.

2 We will first review forms of rapidly
3 destructive arthropathies that have more well-
4 defined phenotypes, including osteonecrosis and
5 Charcot neuroarthropathy. Next, we will review
6 other potential phenotypes that are less
7 well-defined, including analgesic hip and rapidly
8 progressive osteoarthritis.

9 Osteonecrosis is a potential cause of rapid
10 and severe joint destruction. The definition of
11 osteonecrosis is death of bone, leading to collapse
12 of the architectural bony structure. Osteonecrosis
13 can be a primary process or, as we have seen with
14 OA, it can be a secondary process in a setting of
15 severe joint damage. Additional terms used to
16 describe osteonecrosis include avascular necrosis,
17 ischemic necrosis, and asept necrosis of the bone.
18 I will use the term "osteonecrosis."

19 There are limited data on the incidence of
20 osteonecrosis. In the United Kingdom, the
21 estimated incidence was 3 per 100,000 persons in
22 2003. Osteonecrosis is associated with a variety

1 of conditions and medications, including
2 corticosteroids and bisphosphonates.

3 Similarly to OA, osteonecrosis is a
4 heterogeneous disease. The primary factor
5 influencing clinical features of osteonecrosis is
6 the size and location of the necrotic area. In
7 addition, the presence of underlying risk factors
8 influences the manifestations and patterns of the
9 disease. I will focus on patients who have
10 idiopathic osteonecrosis.

11 Patients generally present due to pain, and
12 the femoral head is the most common location of
13 osteonecrosis. However, any skeletal site can be
14 affected. In patients without risk factors, this
15 is generally thought of as a unilateral process
16 without a pattern of joint involvement.

17 In its earliest stages of disease, plain
18 radiographs are generally normal. Later, findings
19 can include the crescent sign and femoral head
20 collapse. This pathologic specimen from the
21 femoral head demonstrates a hyperemic rim and
22 subchondral collapse, which could appear as a

1 crescent sign on radiographs. Pathological
2 specimens primarily demonstrate necrosis, but can
3 also have secondary degenerative features.

4 This table presents a summary of an FDA
5 analysis of osteonecrosis events from a pool of
6 four large NSAID studies. Only patients with OA
7 from these studies were included in this analysis.
8 There were 52,945 patients with OA enrolled in
9 these clinical studies. The population included
10 mostly white females in their 60s. Using adverse
11 event terms, FDA identified only 11 cases of
12 osteonecrosis, with an event rate of 0.2 events per
13 1,000 patient years. Thus, osteonecrosis adverse
14 events appear rare in previous NSAID clinical
15 trials.

16 Evidence suggests that the rate of
17 progression of osteonecrosis is high, particularly
18 among symptomatic patients. A retrospective review
19 of 50 osteonecrotic femoral heads found that
20 67 percent had progressed to femoral head collapse
21 and 68 percent required replacement within a mean
22 of 16 months. However, the size and location of

1 the necrotic area helped predict time to collapse,
2 and thus are key determinants of the natural
3 history of osteonecrosis.

4 The next form of rapidly destructive
5 arthropathy that we will review is Charcot
6 neuroarthropathy. Charcot neuroarthropathy is a
7 potentially rapid and destructive disease. It was
8 first described in association with tabes dorsalis
9 in a setting of syphilis. Subsequently, it has
10 been described with numerous sensory neurological
11 disorders. Currently, diabetes mellitus is the
12 most commonly associated condition with Charcot
13 neuroarthropathy.

14 There are limited data on the epidemiology
15 of Charcot neuroarthropathy, and the incidence and
16 prevalence depends on the population evaluated.
17 While it is clearly associated with sensory
18 neuropathies, approximately 30 percent of cases had
19 no apparent neurological disease in one
20 retrospective case series. Non-clinical data
21 suggests the severity of the neuropathy and the
22 amount of physical activity are not risk factors

1 for the development of Charcot neuroarthropathy.

2 In acute Charcot neuroarthropathy, there is
3 a mild to moderate degree of pain accompanied by
4 edema, warmth, and erythema of the affected area.
5 In one study of 55 diabetic patients, 76 percent
6 reported pain even though they were insensate on
7 physical examination. In addition, 22 percent
8 reported trauma within one month of the onset of
9 symptoms. However, the trauma was minor compared
10 to the amount of joint destruction seen.

11 The pattern of joint involvement depends on
12 the primary neurological process. Patients with
13 syringomyelia develop a neuroarthropathy of the
14 shoulders and elbows, while patients with diabetes
15 mellitus develop a neuroarthropathy of the foot and
16 ankle.

17 A key radiographic feature of Charcot
18 neuroarthropathy is the extent of bony destruction.
19 This radiograph is a lateral study of the knee that
20 shows advanced changes of Charcot neuroarthropathy
21 in a patient with longstanding tabes dorsalis. The
22 image demonstrates gross disorganization of the

1 joint. The articular surfaces appear irregular and
2 eroded. Extensive new bone formation, soft tissue
3 calcification, ossification, and debris are
4 present. There is a massive projection of bone
5 extending from the anterior surface of the tibia.

6 Pathology can reveal osteonecrosis and
7 degenerative changes. Synovial biopsy may reveal
8 particles of dead bone and cartilage embedded in
9 the synovium, secondary to the severity of the
10 joint destruction.

11 The natural history of the disease depends
12 on many factors, including the underlying
13 neuropathy and its timing and extent of treatment
14 interventions. The natural history can be divided
15 into two phases which have substantial overlap.
16 The acute phase is characterized by acute
17 inflammation of the joint. The chronic phase is
18 characterized by established deformity. The
19 progression from acute to chronic can be rapid,
20 with considerable damage occurring in less than six
21 months.

22 The next potential forms of rapidly

1 destructive arthropathy that we will review are the
2 descriptive terms, analgesic hip and rapidly
3 progressive osteoarthritis.

4 A severe form of destructive arthropathy was
5 initially described in the 1960s as analgesic hip.
6 This appeared to be occurring in patients taking
7 NSAIDs, especially indomethacin. Many of the
8 patients were taking NSAIDs for uncomplicated OA
9 and then developed rapid and unexpected hip
10 destruction. Cases of apparent analgesic hip were
11 subsequently described in patients who were not
12 taking any medications. Thus, the pathophysiology
13 of this potential phenotype of rapid joint
14 destruction is unclear.

15 On the right side of the screen, there is an
16 anterior posterior radiograph of the pelvis showing
17 pronounced osteolysis, to the point where the
18 femoral heads have become invisible. This process
19 has also been termed disappearing hips.

20 After performing an extensive literature
21 search, we were able to identify a limited number
22 of retrospective case series and case reports of

1 another form of rapidly destructive arthropathy
2 that is most frequently described in the hips.
3 This process has been given a variety of names,
4 including rapidly progressive osteoarthritis,
5 rapidly destructive arthritis, and rapidly
6 destructive hip disease.

7 It is considered by some to represent a
8 subtype of osteoarthritis. However, there are no
9 validated criteria for this type of rapidly
10 destructive arthropathy, and it is not recognized
11 by the American College of Rheumatology as a
12 specific disease or disease subtype. In addition,
13 there is no standard definition used in the
14 literature. Frequently, the criteria are
15 descriptive, focusing on the severity of joint
16 destruction without a clear etiology.

17 Other case series have used criteria based
18 on the amount of joint space loss. Some case
19 series have used a cutoff of at least 2 millimeters
20 of joint space loss within one year. However, no
21 standard criteria are used for the term rapidly
22 progressive OA.

1 In addition, each sponsor used a distinct
2 definition of rapidly progressive OA in its
3 adjudication process. In Pfizer's adjudication in
4 pink, rapidly progressive OA was divided into two
5 types. The first type focused on the amount of
6 joint space narrowing in one year. The second type
7 required abnormal loss or destruction of bone that
8 is not normally present in end-stage OA. These
9 findings were described as catastrophic bone
10 failure.

11 In yellow, you see the definition of rapidly
12 progressive OA used by Janssen. This definition
13 focused on the amount of joint space narrowing. In
14 blue are Regeneron's adjudication categories.
15 Regeneron did not provide a definition for rapidly
16 progressive OA. Rather, if a reviewer determined
17 that evidence suggested a diagnosis other than OA,
18 then they were asked to provide a diagnosis. Thus,
19 the one case of joint destruction that was labeled
20 as possible rapidly progressive OA in the Regeneron
21 development program had features that were not
22 consistent with normal OA progression.

1 In the literature, rapidly destructive OA
2 refers to rapid joint destruction with primarily
3 degenerative features. This anterior posterior
4 radiograph shows the rapid progression of this
5 disease from mild OA changes to severe joint
6 destruction over six months. The image on the left
7 displays typical changes of OA. The image on the
8 right was obtained six months later. It shows
9 severe flattening of the femoral head with an
10 eccentric depression of the lateral articular
11 surface associated with superior lateral
12 subluxation, sclerosis, and subchondral defects.
13 In addition, the femoral head has a hatchet-like
14 appearance.

15 The term "rapidly progressive OA" is a
16 descriptive term for a process that has
17 similarities and differences with OA. The
18 processes are similar, as both have primarily
19 degenerative changes on histology. However, there
20 are many differences between these processes.
21 First, rapidly progressive OA is usually described
22 as occurring in a normal joint that is not painful

1 at baseline. Thus, there does not appear to be a
2 mechanism by which patients could be screened for
3 being at high risk for the development of rapidly
4 progressive OA.

5 Second, the rate of joint destruction is
6 much more rapid and severe than what is generally
7 seen in OA. In a large clinical trial of
8 risedronate, in 2,483 individuals with knee OA, the
9 rate of joint space loss associated with rapidly
10 progressive OA was not seen in any subject.

11 Third, the radiographic features of rapidly
12 progressive OA are atypical for OA. These features
13 include the lack of osteophytes and the presence of
14 subchondral insufficiency fractures.

15 Using Pfizer's definition, it appears that
16 rapidly progressive OA is a rare occurrence in a
17 community-based cohort in another trial sponsored
18 by Pfizer. A member of the tanezumab adjudication
19 committee reviewed knee radiographs from the
20 progression cohort of the Osteoarthritis Initiative
21 Study. A total of 1,174 patients with follow-up
22 radiographs were evaluated. Rapidly progressive OA

1 was identified in a total of 3.5 percent of
2 participating subjects.

3 An important observation is that the
4 majority of these patients fit the criteria for
5 rapidly progressive OA because of changes in joint
6 space and thus were classified as type 1 rapidly
7 progressive OA. In contrast, only .2 percent of
8 patients had type 2 rapidly progressive OA, which
9 is defined as bone destruction not normally present
10 in end-stage OA.

11 A similar analysis was conducted in 1,457
12 patients with knee OA who participated in a
13 two-year Pfizer study of radiographic progression.
14 This study did not involve the administration of
15 anti-nerve growth factor agents. Patients had knee
16 OA with baseline Kellgren-Lawrence grades of 2 or
17 3. Patients underwent x-ray evaluations annually.
18 1.1 percent of participants developed rapidly
19 progressive OA and just .1 percent were classified
20 as type 2 rapidly progressive OA. Thus, in two
21 distinct patient populations, an arthropathy-
22 causing rapid joint destruction is unusual in OA

1 patients.

2 Potential forms of rapidly destructive
3 arthropathies have overlapping features, such as
4 degeneration and necrosis. Thus, it is frequently
5 difficult to assess what is the primary process,
6 limiting our understanding of the pathophysiology.

7 The categories I have reviewed are somewhat
8 artificial, given these overlapping features, and
9 it is important to highlight that the primary
10 concern is a poor patient outcome. There have been
11 numerous hypothesized mechanisms of joint injury,
12 including drug toxicity and subchondral
13 insufficiency fractures. However, the pathogenesis
14 is not well understood.

15 In conclusion, the majority of patients with
16 OA have a slowly progressive course. A small
17 subset of patients may have more rapid progression,
18 but it is unusual for patients with OA to have
19 rapid and severe joint destruction. Thus, rapidly
20 destructive arthropathies represent joint
21 destruction not normally seen in OA.

22 Now, Dr. Pokrovnichka will review safety and

1 efficacy data of the anti-nerve growth factor
2 agents.

3 **FDA Presentation - Anjelina Pokrovnichka**

4 DR. POKROVNICHKA: Good morning. My name is
5 Anjelina Pokrovnichka, and I'm a medical reviewer
6 in the Division of Anesthesia, Analgesia, and
7 Addiction Products. My presentation will outline
8 the investigation of products, summarize the
9 overall safety profile of the anti-nerve growth
10 factor agents, focus in on joint-related adverse
11 events, and finally, briefly describe the efficacy
12 of complete phase 3 osteoarthritis trials with
13 tanezumab. As already described by the sponsors,
14 these are the three products under investigation
15 and discussion.

16 You have heard about the regulatory history
17 from Dr. Rappaport. I will skip this for now, but
18 can answer questions if you have them later.

19 Slide 44. As already described by the
20 sponsors, anti-nerve growth factor drugs have been
21 studied in a variety of painful conditions, with
22 the highest exposure coming from osteoarthritis

1 trials. Pfizer's osteoarthritis program is in the
2 phase 3 phase of development, with over 10,000
3 patients enrolled, while both Janssen and Regeneron
4 are in phase 2 of development, with a smaller
5 number of patient exposures.

6 In the next several slides, I will briefly
7 describe events of concern from the overall safety
8 profile of the anti-nerve growth factor agents.

9 The following adverse events appear to be
10 study drug related, neurosensory symptoms,
11 arthralgia, pain in extremities, and peripheral
12 edema. These events were described for all
13 anti-nerve growth factor agents. The long-term
14 consequences are unknown.

15 The development of abnormal peripheral
16 sensation with anti-nerve growth factor treatment
17 was noticed early in drug development. Paresthesia
18 was the most commonly reported symptom. These
19 events were mild to moderate in severity, occurred
20 relatively early, within several weeks post-dosing,
21 and appeared dose-related. Although these adverse
22 events were generally reversible, there have been

1 cases with persistent symptoms for over five
2 months.

3 On this table, if you look across each row,
4 you can see that the frequency of peripheral edema,
5 arthralgia, pain in extremities, and paresthesias
6 are higher compared to placebo and naproxen, and
7 increases with increasing doses of tanezumab.

8 There were generally higher rates of arthralgia,
9 pain in extremities, and paresthesias with
10 fulranumab than oxycodone and placebo. The limited
11 exposure makes it difficult to comment on the
12 presence of a clear dose response.

13 I will continue with joint-related adverse
14 events. Details were already presented by the
15 sponsors, and in order not to be redundant, I will
16 only highlight areas of the agency's concerns.

17 This slide illustrates that the proportion
18 of subjects with baseline Kellgren-Lawrence grades
19 of 3 and 4 in anti-nerve growth factor
20 osteoarthritis trials was similar to the
21 osteoarthritis initiative study progression cohort.
22 The median disease duration was between 5 and

1 8 years in the clinical trials. This is an
2 important point to keep in mind when considering
3 the extent of destructive arthropathy observed in
4 the clinical trials.

5 Although, overall, the total number of joint
6 replacement cases appears comparable across
7 placebo, active comparator, and anti-nerve growth
8 factor treatment groups, within the tanezumab
9 treatment groups there was a dose response.

10 This table provides some details of the dose
11 response for overall total joint replacement
12 presented here as events per 100 patient years.
13 The data in the blue box, or the smaller box,
14 reflects the result in controlled monotherapy
15 studies, with the lowest rates of total joint
16 replacements and no apparent dose response. The
17 risk of joint replacement is greater with longer
18 duration of anti-nerve growth factor exposure and
19 is even greater when non-steroidals were used
20 concurrently, as seen in the red box or the bigger
21 box, as appeared on the screens. The dose response
22 is most evident when tanezumab is combined with

1 non-steroidals and in the non-controlled,
2 long-term, osteoarthritis studies.

3 This slide illustrates that the joints
4 involved included unusual joints such as shoulder
5 and ankle. There was a higher rate of total joint
6 replacements for fulranumab compared to placebo in
7 a study of knee and hip osteoarthritis, where
8 fulranumab was added to existing analgesics,
9 including non-steroidals but similar to oxycodone
10 in a second study of knee OA.

11 I will move on to the reported events of
12 osteonecrosis. The signal was first adjusted by
13 investigator reports. It was concerning because
14 this has not been seen on osteoarthritis trials
15 with other analgesics. The diagnosis was based
16 primarily on imaging findings and surgical reports.

17 Unfortunately, histopathology was available
18 in only a small number of cases. However, in some,
19 the histopathology was confirmatory. In addition,
20 there were cases with multiple joints with
21 osteonecrosis, non-indexed joints involved, unusual
22 joints such as shoulder and foot, and in some

1 patients who had no history of osteoarthritis.

2 This slide presents data from tanezumab and
3 illustrates that -- is shown in the red box -- in
4 half of the cases of osteonecrosis reported in
5 osteoarthritis patients, the joint with reported
6 osteonecrosis was not the index joint and included
7 unusual joints such as shoulder and foot.

8 These are the reported number of cases of
9 osteonecrosis that are based on updated information
10 submitted by Pfizer and Janssen, that are
11 investigator-reported cases, nearly in all patients
12 who received study drug. There were no reports for
13 osteonecrosis from Regeneron.

14 I will continue my presentation with the
15 discussion of the sponsors' adjudication of the
16 joint replacement cases. Adjudication of the joint
17 replacement cases was performed by the sponsors,
18 and the results have been already presented.

19 In order to determine whether we are in
20 agreement with the adjudication conducted by the
21 sponsors, the agency had two separate adjudications
22 of the joint replacement cases conducted, one

1 internal to the agency and one by an external
2 academic expert.

3 The approach taken by the agency
4 adjudicators was similar, but not identical to that
5 taken by the sponsors. Recognized limitations
6 included the lack of consistent availability of
7 histopathology and baseline imaging. The external
8 adjudicator also did not have access to the
9 electronic imaging files.

10 The methods and the results of the agency
11 adjudications will be presented later today. I
12 will focus my presentation on findings from
13 sponsors' adjudications.

14 A signal of rapid and unexpected joint
15 deterioration requiring joint replacement surgery
16 was noted in the tanezumab and fulranumab clinical
17 programs. Rapidly progressive osteoarthritis was
18 an adjudication definition used by the sponsors.
19 However, as Dr. Maynard pointed out, this is a
20 descriptive term, not uniformly recognized as a
21 diagnostic entity in the rheumatology community.

22 The incidence of rapid joint destruction

1 events was highest in anti-nerve growth factors
2 with non-steroidal treatment groups, followed by
3 anti-nerve growth factor monotherapy, and much
4 lower in patients exposed to placebo or active
5 comparators. These events usually occurred after
6 several doses of study drug. It is important to
7 point out that it was not restricted only to
8 advanced osteoarthritis cases, but also occurred in
9 patients who entered the clinical studies with
10 Kellgren-Lawrence grades of 2.

11 This slide provides the adjudication
12 outcomes for rapidly progressive osteoarthritis
13 from phase 3 tanezumab osteoarthritis studies.
14 Pfizer defined rapidly progressive osteoarthritis
15 type 1 as more than 1 millimeter joint space
16 narrowing over the course of one year and rapidly
17 progressive osteoarthritis type 2 as abnormal or
18 destruction of bone that is not normally present in
19 end-stage OA.

20 There are two incorrect numbers. The 19
21 should be 14 and 24 should be 19 in the tanezumab
22 monotherapy column, for your notes. However, my

1 conclusions remain the same.

2 There were no cases in patients receiving
3 placebo treatment and only one case from the active
4 comparator group who were adjudicated by Pfizer as
5 rapidly progressive osteoarthritis. More patients
6 from the tanezumab monotherapy group compared to
7 active comparator had rapidly progressive
8 osteoarthritis adjudicated joints, and the number
9 further increased when tanezumab was used in
10 combination with non-steroidals.

11 Using Pfizer's definition for rapidly
12 progressive osteoarthritis, this slide compares the
13 rapidly progressive osteoarthritis occurrence in
14 tanezumab osteoarthritis trials to community-based
15 cohorts and other trials sponsored by Pfizer that
16 Dr. Maynard has already described in her talk.

17 An important observation is that most of the
18 patients in the tanezumab trials met the definition
19 for rapidly progressive osteoarthritis type 2.
20 That includes destructive changes not normally
21 present in osteoarthritis, compared to the
22 osteoarthritis initiative study and the

1 radiographic progression cohort study of Pfizer,
2 where the majority of the patients fit the criteria
3 for type 1 for joint space narrowing.

4 This slide illustrates that, for those
5 patients with available baseline imaging, rapidly
6 progressive osteoarthritis was not restricted only
7 to advanced osteoarthritis, but also occurred in
8 patients with a Kellgren-Lawrence grade of 2.

9 Also, there was a substantial number of patients
10 for whom the baseline Kellgren-Lawrence grade for
11 the surgery joint was not available.

12 In the fulranumab program, looking at the
13 highlighted column, all adjudicated rapidly
14 progressive osteoarthritis cases received
15 fulranumab. There were no cases adjudicated as
16 rapidly progressive osteoarthritis from the placebo
17 and oxycodone groups. The adjudicated rapidly
18 progressive osteoarthritis cases in the fulranumab
19 studies also occurred in joints with Kellgren-
20 Lawrence grades of 2, 3, and 4.

21 For Regeneron, from 509 patients, 14 events
22 of joint replacements were reported in 12 subjects.

1 Only 1 of the 14 joint replacements was adjudicated
2 as possible rapidly progressive osteoarthritis.

3 The following two slides present sponsors'
4 analysis for events of fractures. This slide
5 illustrates the higher event rates for fractures in
6 tanezumab-treated patients in phase 3
7 osteoarthritis studies. No pathological fractures
8 were described, but the subcategory of unspecified
9 fractures includes cases for which no trauma
10 preceding the event of fracture was reported.

11 Similar findings for the fracture events
12 were observed for fulranumab. In addition, two
13 cases of pathological fractures from patients
14 exposed to fulranumab were reported. For
15 Regeneron, there were two reports of traumatic
16 fractures in patients who received RGN475.

17 In the following several slides, I will
18 briefly summarize efficacy findings from selected
19 phase 3 osteoarthritis studies with tanezumab.

20 The team statistician, Dr. Jonathan Norton,
21 evaluated the methods and results for five phase 3
22 osteoarthritis studies for tanezumab. Based on the

1 submitted information, he determined that the
2 statistical methods were acceptable, and tanezumab
3 appeared to be efficacious.

4 The following slides show results from three
5 studies that included an active control, either
6 naproxen or celecoxib. For each study, we show
7 results for change in baseline from WOMAC pain and
8 function at 16 weeks. These were two of the three
9 primary endpoints, the third being the WOMAC
10 patient global assessment. The figures shown are
11 based on the results provided by Pfizer.

12 Study 1015 was a 24-week study of patients
13 with osteoarthritis of the knee, with a Kellgren-
14 Lawrence grade of 2 or higher. Subjects had to
15 discontinue medications taken for osteoarthritis
16 pain prior to the initial pain assessment. At
17 baseline, a WOMAC pain subscale score of 5 or
18 higher for the index knee was required.

19 Subjects were randomized to one of four
20 treatment groups: placebo, naproxen, tanezumab 5
21 milligrams, and tanezumab 10 milligrams. The
22 change from baseline in the WOMAC pain subscale to

1 week 16, after two doses of study drug, was the
2 primary efficacy measure.

3 Displayed here is a continuous responder
4 plot. The X axis shows the percent improvement in
5 pain from baseline. The Y axis shows the percent
6 of subjects. The curves show the percentage of
7 patients who achieved any given percent improvement
8 of pain at week 16 of the study. Subjects who
9 discontinued the study before week 16 are assigned
10 zero percent improvement.

11 You can see that there is overlap of the
12 tanezumab 5- and 10-milligram curves and that
13 compared to naproxen, tanezumab has about the same
14 percentage of patients, with a 30 percent
15 improvement in pain and a slightly greater
16 percentage, with a 50 percent improvement in pain.

17 The bar chart shows the mean change from
18 baseline to week 16 in WOMAC pain, shown in blue,
19 and function, shown in red, by treatment group.
20 The tanezumab 5-milligrams and 10-milligram doses
21 were statistically superior to placebo on both pain
22 and function. Both doses of tanezumab resulted in

1 numerically large improvements in pain and function
2 when compared to naproxen.

3 Study 1018 was similar in design to study
4 1015, except that patients with both hip or knee
5 osteoarthritis were enrolled. The figure presented
6 is a continuous responder plot similar to that
7 shown for study 1015. Tanezumab 5 milligrams,
8 appears to have a greater percentage of patients
9 achieving both 30 and 50 percent improvement in
10 pain at week 16, compared to tanezumab
11 10 milligrams and naproxen. And all drugs had a
12 greater percentage of patients with 30 and
13 50 percent improvement in pain than placebo.

14 In study 1018, the tanezumab 5- and
15 10-milligram doses were statistically superior to
16 placebo on both pain and function. As with study
17 1015, both doses of tanezumab resulted in a
18 numerically larger improvement in pain and function
19 when compared to naproxen.

20 Study 1025 was a 56-week study in patients
21 with osteoarthritis of the hip or knee, with a
22 Kellgren-Lawrence grade of 2 or higher. Treatment

1 groups included tanezumab monotherapy,
2 non-steroidal monotherapy, and a combination of
3 tanezumab with non-steroidals.

4 Study drug was administered every eight
5 weeks, for a total of seven doses. Subjects were
6 required to be on a stable dose of naproxen or
7 celecoxib for 30 days prior to screening with some
8 improvement of the OA index joint pain, but still
9 requiring additional pain relief. The change from
10 baseline in WOMAC pain subscale to week 16, after
11 two doses of study drug, was the primary efficacy
12 measure.

13 Study 1025 was put on clinical hold.
14 However, the primary endpoints were not affected.
15 This study had two cohorts, one for patients on
16 naproxen, one for patients on celecoxib. Results
17 are displayed for the naproxen cohort. The
18 celecoxib cohort had similar results for these
19 endpoints.

20 This responder plot shows that all tanezumab
21 treatment groups were comparable in terms of
22 percentage of patients achieving 30 and 50 percent

1 improvement in pain at week 16, with no apparent
2 benefit from concomitant use of non-steroidals.
3 All tanezumab treatment groups, either with or
4 without non-steroidals, appeared to have a greater
5 percentage of patients achieving 30 and 50 percent
6 improvement than naproxen alone. The results for
7 the celecoxib analysis were similar.

8 This bar chart shows the mean change from
9 baseline to week 16 in WOMAC pain and function
10 subscales by treatment group in study 1025. There
11 was only a small difference associated with the
12 addition of the non-steroidal to tanezumab in terms
13 of change in pain and function. The tanezumab
14 10 milligrams plus naproxen arm achieved
15 statistically significant differences in both pain
16 and function when compared to the naproxen-only
17 arm. The tanezumab monotherapy arm, as well as the
18 tanezumab 5 milligrams plus naproxen arm all
19 yielded numerically large improvements in pain and
20 function compared to naproxen.

21 To summarize, there is a safety signal for
22 joint destruction with the administration of the

1 anti-nerve growth factor agents. The events of
2 rapid joint destruction occur in patients exposed
3 to anti-nerve growth factor agents alone and at
4 doses associated with efficacy. The signal is even
5 greater with concurrent non-steroidal use. The
6 efficacy data from tanezumab suggests a numerically
7 larger effect size relative to non-steroidals.

8 Thank you.

9 Now, Dr. Colburn will give her presentation.

10 **FDA Presentation - Nona Colburn**

11 DR. COLBURN: Good morning. My name is Nona
12 Colburn. I'm a medical officer in the division
13 that evaluates orthopedic devices in the Office of
14 Device Evaluation in the Center for Devices and
15 Radiological Health. I will be reporting FDA's
16 adjudication results and analyses for the anti-
17 nerve growth factor product, hereafter referred to
18 as anti-NGF.

19 To demonstrate the safety and effectiveness
20 of anti-NGF in the control of pain, several multi-
21 center, prospective, randomized, concurrently
22 controlled studies were designed for patients with

1 KL-graded osteoarthritis of the hip and/or knee or
2 chronic low back pain, to receive either placebo,
3 NSAIDs, or one of these three therapeutic agents.

4 The purpose of this adjudication is to
5 evaluate reported cases of patients who were
6 suspected of having osteonecrosis and/or who
7 required surgical intervention for total joint
8 replacements. My discussion will focus on the key
9 aspects of the adjudication process.

10 Overall, there were 355 cases and 401 joints
11 from three different sponsors that were reviewed.
12 The assessment was blinded to both the treatment
13 received and to the sponsors' own adjudicated
14 responses. Joints were assigned one of five
15 adjudicated categories: normal progression of
16 osteoarthritis, rapid progression of
17 osteoarthritis, osteonecrosis, other with a
18 diagnosis specified, and insufficient information.
19 The table depicts the number and percentage of each
20 joint assigned to their respective categories.

21 In assigning an adjudication category, I
22 utilized clinical, radiological, and pathological

1 assessments to evaluate the clinical progression of
2 each joint from baseline enrollment, the time at
3 which the patient received the first study dose, to
4 the onset of event, the discovery of osteonecrosis,
5 and/or the date of joint replacement.

6 From the original datasets, I reviewed
7 digital imaging, imaging reports, pathology,
8 pathology reports, medical history narratives found
9 in operative reports, consultation reports, and
10 history, and physicals, as well as MedWatch reports
11 and case report forms.

12 Next, I would like to discuss briefly the
13 principles used in making a clinical decision for
14 each adjudication category. By definition,
15 osteoarthritis is a slowly progressive joint
16 degeneration. To assign a joint the adjudicated
17 category of normal progression of OA, the past
18 medical history should be consistent with
19 longstanding disease and a general lack of
20 confounding co-morbidities. Patient demographics
21 should reflect, in the overall clinical
22 presentation, risk factors such as age, obesity, or

1 a prior history of trauma.

2 To distinguish NPOA from other adjudication
3 categories, radiographic and pathologic features
4 played a key role. Kellgren-Lawrence scores were
5 assessed by reviewing digital imaging and/or
6 radiology reports taken at baseline enrollment and
7 compared to those taken at the time of the event.

8 In the case where concomitant OA and ON were
9 observed on pathological specimens, normal
10 progression of osteoarthritis was considered if the
11 predominant features suggested OA, but
12 osteonecrosis if the predominant features suggested
13 ON.

14 Based on that which was described in the
15 literature, and the sponsors' own adjudication
16 summaries, and given the fact this RPOA is a poorly
17 defined disease entity, as discussed by
18 Dr. Maynard, the assignment of RPOA as an
19 adjudication category was considered not as a
20 definitive diagnosis, but rather as a catchment
21 terminology to describe a specific clinical
22 presentation. Therefore, RPOA was considered if a

1 patient presented with severe pain and an
2 abnormally rapid rate of bony destruction or
3 significant loss of joint space, for example, a
4 dramatic change in KL grade from the baseline
5 imaging and/or reports compared to those taken
6 post-exposure. Moreover, there should be no
7 evidence of any other forms of rapidly destructive
8 arthropathy.

9 Cases that presented with confounding
10 diagnoses such as steroid use, neuropathic
11 osteoarthropathy, rheumatoid and seronegative
12 arthritis, primary osteonecrosis, septic arthritis,
13 and chondrocalcinosis, were evaluated and excluded.

14 Because of ongoing chondrolysis and
15 progressive bony destruction, the radiographic
16 features of cases assigned to RPOA were
17 characteristic. However, in order to make the
18 assignment, comparator x-rays and/or radiology
19 reports were necessary in order to establish a
20 timeline.

21 Some of the radiographic features seen in
22 this adjudication were greater than 50 percent

1 joint space narrowing in one year, abnormal marked
2 bony resorption with bone loss, flattening or
3 absence of the femoral head, condyles or tibial
4 plateau, and a lack of clear demarcation between
5 necrotic and healthy bones. The MRIs often showed
6 some chondral insufficiency fractures.

7 In review of pathology specimens and/or
8 reports, there was a general lack of information,
9 with no evidence for osteonecrosis. Severe
10 degenerative changes in articular cartilage, and
11 subchondral detritus, and bony fragmentation, and
12 debris were commonly observed, along with reactive
13 synovitis.

14 The diagnosis of osteonecrosis was
15 considered in a literal and de facto sense.
16 Specifically, if characteristic MRI and pathologic
17 descriptions demonstrated the presence of bony
18 death, the case was adjudicated as osteonecrosis.
19 However, in determining whether osteonecrosis was
20 felt to be primary or secondary, and more
21 specifically, whether OAN was felt to be drug
22 related, the overall clinical presentation was

1 considered, in particular, at-risk co-morbidities
2 and medications.

3 As with RPOA, the radiographic and
4 pathologic features of cases adjudicated to ON were
5 characteristic. Seen on radiographs were cystic or
6 sclerotic changes and collapse or change in contour
7 of the femoral head, condyles, or tibial plateau.
8 The pathognomonic crescent sign was observed in a
9 few of the cases. However, plain radiographic
10 imaging was not as definitive for the diagnosis of
11 ON as were these characteristic MRI findings seen
12 and described with several of the cases.

13 Pathology is the gold standard for the
14 diagnosis of osteonecrosis, and histologically
15 proven dead bone in a few of the cases stood alone
16 to make the diagnosis. As discussed previously,
17 degenerative changes were seen secondarily, but
18 cases were adjudicated as ON when the predominant
19 features were that of necrosis. The only exception
20 was in the case of end-stage OA, associated with
21 severe cystic disease and chronic ON. These were
22 adjudicated as other.

1 Cases were adjudicated as other when another
2 diagnosis, not definitively assessed as any of the
3 other three categories, was apparent. Such
4 examples included failed lumbar hardware, different
5 types of fracture, rotated cuff, tendinopathy, and,
6 as previously noted, end-stage OA associated with
7 severe cystic disease and chronic ON.

8 As previously mentioned, the availability of
9 baseline and/or post-study imaging and/or reports
10 were critically important in definitively assigning
11 an adjudication category that depended on rate of
12 change, such as NPOA or RPOA. When this
13 information was not available, the case was deemed
14 insufficient to make a decision.

15 Of the 355 cases and 401 joints, the
16 majority of joints involved the adjudicated
17 diagnosis of NPOA, with a significant number of
18 RPOA and ON cases, 28 percent, as depicted in this
19 graph.

20 The possible relatedness of the contribution
21 of study drug to the adjudicated diagnosis was
22 blindly determined independently by considering all

1 components of the case presentation, using clinical
2 judgment and insight. Drug, as a contributing
3 factor, was felt to be more likely in cases of RPOA
4 and ON and less likely in cases of NPOA, as
5 depicted in the table and the following graph.

6 Drug doses, administration, and trial design
7 differed among the three sponsors. However, as
8 depicted in the tables that will follow, lower
9 doses and/or less frequent administration of
10 anti-NGF, as well as placebo, were more likely
11 associated with NPOA. Higher doses and the
12 addition of NSAIDs with higher doses were more
13 likely associated with RPOA and ON.

14 As this table shows, this trend is the most
15 apparent with Pfizer, given the larger number of
16 cases and treatment groups. With Janssen, the
17 numbers were lower. And cases of RPOA and ON were
18 observed in treatment arms with higher doses and
19 more frequent drug administration only in those
20 treatment groups with a significant number of
21 patients to make the observation. Because of the
22 very few number of cases with Regeneron, this trend

1 was not observed. It is, however, noted that no
2 cases of ON or RPOA was reported in the placebo
3 group.

4 The overall level of agreement with the
5 sponsors' adjudication was determined by comparing
6 the FDA-adjudicated diagnosis to the sponsors'
7 unblinded adjudication responses and assigning a
8 binomial determination. A breakdown of the level
9 of agreement is shown in the table. Note that
10 there is a general agreement on cases adjudicated
11 to RPOA.

12 Overall, there was considerable agreement
13 between FDA and sponsors' adjudications. Although
14 each sponsor has specified methods of adjudication,
15 their diagnostic conclusions were more likely to
16 differ in cases of osteonecrosis and insufficient
17 information, as noted in the chart.

18 The major reason for these divergences were,
19 one, osteonecrosis was diagnosed by FDA if clear
20 pathological and/or imaging criteria was met and,
21 two, insufficient information was the adjudicated
22 response if no baseline, or post-study imaging, or

1 imaging reports were available. It was noted that
2 Pfizer was more likely to consider the diagnosis of
3 RPOA and spontaneous osteonecrosis of the knee over
4 that of the adjudicated category of osteonecrosis.

5 Shown here are the pre- and post-exposure
6 x-rays of a case of RPOA of the right hip that
7 occurred within eight months of receiving tanezumab
8 10 milligrams plus NSAID. Note on the post-
9 exposure film the partial dissolution of the
10 femoral head. Both FDA and the sponsors'
11 adjudicated diagnoses agreed.

12 Shown here are the pre- and post-exposure
13 x-rays of an adjudicated case of RPOA occurring in
14 both hips within 10 months of drug exposure.
15 Although in this case, a concomitant NSAID was not
16 part of the study arm, the medical history revealed
17 ongoing diclofenac use, and both the FDA and the
18 sponsors' adjudicated diagnoses agreed.

19 Shown here are the pre- and post-exposure
20 x-rays of an FDA-adjudicated case of osteonecrosis
21 occurring in the medial femoral condyle of the
22 right knee within six months of receiving tanezumab

1 10 milligrams plus NSAID.

2 The right knee in this case was the index
3 joint, and the baseline x-ray was read as KL
4 grade 2. MRI of the right knee, taken one month
5 prior to the post-exposure film, was read as
6 possible spontaneous osteonecrosis of the internal
7 femoral condyle. The sponsor adjudicated this case
8 to other, with a diagnosis of insufficiency
9 fracture, medial femoral condyle.

10 Several cases adjudicated as RPOA
11 demonstrated considerable and rapid destruction,
12 most notably in the femoral head and medial femoral
13 condyle, most often within 6 to 12 months
14 post-exposure, and with dramatic clinical
15 presentations.

16 This type of destructive arthropathy is
17 initiated in an abnormal joint and appears to be
18 more aggressive to bony destruction than that
19 described in previous literature, which classically
20 could appear in a normal joint.

21 Osteonecrosis, analgesic joints associated
22 with NSAID use, and neuropathic arthropathy can all

1 have similar clinical presentations as that seen
2 with the adjudicated RPOA seen in this series. In
3 each of these types of destructive arthropathy, the
4 underlying pathophysiology may be related to
5 improper protective sensory input perhaps when NGF
6 is up-regulated locally in painful osteoarthritis
7 conditions at the joint site. This could explain
8 any synergistic effect noted with NSAID use.

9 In conclusion, I considered the adjudicated
10 cases of RPOA seen with drug exposure to anti-NGF
11 to be a unique clinical form of rapidly destructive
12 arthropathy over and above that seen in the normal
13 progression of osteoarthritis. Thank you.

14 DR. BUCKLEY: Thank you, Dr. Colburn. We're
15 going to break for lunch now. We're going to save
16 questions for the FDA until the end of the FDA
17 presentation, after lunch. We're on a tight
18 schedule. I'd like to propose that we meet here
19 again at 12:45, a 45-minute lunch; we'll reconvene.

20 Some reminders. Take any personal
21 belongings you have that you're going to need with
22 you because the room will be secured, and you won't

1 be able to get back in until the meeting
2 reconvenes. And a reminder to panel members,
3 please remember that there should be no discussion
4 of the meeting topic during lunch, amongst
5 yourselves, or with any members of the audience.

6 Thank you for everybody's hard work this
7 morning, and we'll be back here in 45 minutes.

8 (Whereupon, at 11:56 a.m., a luncheon recess
9 was taken.)

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

(12:45 p.m.)

DR. BUCKLEY: We have a busy afternoon in front of us, so I think we will get started. Before the break, Dr. Bathon will be speaking to us. At the end of that, we'll have time for clarifying questions, both about the presentation from the FDA this morning as well as any questions about Dr. Bathon's presentation. And then we'll move to the open public hearing. So again, we'll start with Dr. Joan Bathon.

Speaker Presentation - Joan Bathon

DR. BATHON: Good afternoon. So I'll just start by saying that I have no disclosures with any of the sponsors nor any other organization, pharmaceutical organization.

So we were asked to provide an independent review of 492 reported adverse events, that either represented total joint arthropathy or, in some cases, osteonecrosis without arthropathy. And as you already have heard, these are participants in pain studies, using tanezumab, fulranumab, and

1 RGN475.

2 The questions that we were asked to address
3 are, would these events be expected on a background
4 of pre-existing OA, since most of the patients had
5 OA? And are these events likely related to study
6 drug or not?

7 As you heard from Dr. Rappaport already,
8 there were a number of limitations in our
9 adjudication of the data. We had a very short
10 timeline, and we had no original images. But what
11 we did have were clinical data and narratives
12 related to the adverse event, but not any primary
13 study data.

14 We had printed copies of joint images. We
15 had printed copies of the pathology images from the
16 electronic files and MRI reports, but we did not
17 have the original images. Often, the radiology
18 images were poor quality and you already saw some
19 of those from the previous presenters, somewhat
20 limited in scope and, again, no MRI images.

21 In view of this, we had no confidence that
22 we could really evaluate whether osteonecrosis was

1 present or not, especially without the MRI images.
2 So therefore, we had a very conservative
3 adjudication process in which images were examined
4 primarily to determine whether severe joint
5 deformity had developed during this study. And
6 this evaluation was focused primarily on bone
7 changes of collapse, impaction, fragmentation,
8 marked subluxation, and resorption.

9 The pathology images, as you've heard, were
10 only available in a minority of cases. We did not
11 have any information on how the tissues were
12 sampled and why we had some images, whether there
13 were additional images that we hadn't received or
14 not. We didn't know if they were sampled from the
15 area of greatest osteoarthritis involvement or from
16 the area of suspected infarct. And again, we only
17 had one or two printed images of varying quality.

18 If osteonecrosis were present on those
19 images, we had confidence that it was a true
20 finding. If it were not present, we had no
21 confidence that we could comfortably rule out
22 osteonecrosis.

1 So I was assisted, as already mentioned, by
2 a musculoskeletal radiologist, a musculoskeletal
3 pathologist, and two of our rheumatology fellows,
4 who went through the entire case reports and
5 accumulated relevant data. So some of those data
6 included demographics, medications, risk factors
7 for osteonecrosis if they were available, baseline
8 and end-of-study markers such as the WOMAC score,
9 and so forth.

10 In terms of the pathology scoring, the
11 pathologist rated it as zero, 1, 2, 3, or 4, zero
12 being neither OA nor a non-OA process. And we use
13 the term non-OA because the changes that we were
14 looking for, we agreed with what's been said
15 before, were not typical of regular, normally
16 progressing osteoarthritis. Number 1 was
17 suspicious for this non-OA process; 2 was just OA;
18 3 was overlapping features of both; and 4 would be
19 indeterminate.

20 We had two outcomes that we looked at.
21 Outcome number 1 was this state of the joint,
22 pre-surgically, so patients who had received drug

1 and were about to have surgery. We assessed for
2 both KL score and for the presence or absence of
3 this "non-OA" process, which we refer to again as
4 the presence or absence of severe joint deformity
5 manifested by osteochondral defects, deformity,
6 collapse, impaction, fragmentation, bone
7 resorption, severe subluxation.

8 While we recognize that these bone changes
9 could also be representative of severe OA, those
10 features weren't typical of OA and, therefore, it
11 raised the question of whether there could be
12 contribution from osteonecrosis, a Charcot-like
13 picture, subchondral fractures, tendon ruptures,
14 and so forth.

15 Our outcome number 2 was a change in the
16 joint. And for this we required that we had a
17 pre-study and pre-surgical film. Again,
18 pre-surgical is the last film available before they
19 had surgery.

20 Assessment was whether they had marked
21 deterioration or not, or it could be indeterminate.
22 We did not use a category called "rapidly

1 progressive OA" because we couldn't assess the
2 change in the joint with any degree of assurance,
3 and we refer to these bony changes as non-OA, not
4 rapidly progressive OA.

5 So when we score it, the radiology images,
6 we were scoring the pre-surgical state as OA only,
7 OA indefinite, or high suspicion for a non-OA
8 process. Number 3 was high suspicion for a non-OA
9 process only, and number 4 was OA, and
10 indeterminate for a non-OA process. The first four
11 are the ones that we mostly saw and focused on, but
12 we included all potential categories here.

13 The scoring for the change in the joint was
14 simple. It was either marked deterioration, or
15 not, or indeterminate. And indeterminate was
16 almost always that there were either no pre-study
17 films or uninterpretable pre-study or pre-surgical
18 films.

19 I've given you a lot of background on
20 limitations of the data that we had, but I want to
21 show you some examples of what we called marked
22 deterioration because, despite some poor quality

1 films, I think they're relatively dramatic and not
2 hard to argue with.

3 So in this film, we see the pre-study knee
4 in January of '09, and about a year later, there's
5 very severe subluxation with marked deterioration
6 of the joint space and fragmentation of bone.

7 In this one, we see a progression of films.
8 And you see moderate OA on the left side, and then
9 some bone fragmentation, and impaction of the
10 tibial plateau in the middle film, and then severe
11 subluxation again with bone fragmentation and
12 impaction.

13 There's another one where we see moderate to
14 severe OA on the left and then subluxation of the
15 joint again with impaction, and a very large
16 osteochondral defect on the medial tibial plateau,
17 and some impaction in the femur.

18 A hip, where there's very advanced OA on the
19 left with subchondral cysts on both sides of the
20 joint, and then osteolysis of the femoral head, and
21 some acetabular bone loss as well; another one
22 where we see fairly advanced OA of the medial

1 compartment on the left, and then a severe
2 impaction, and bone loss with fragmentation; and
3 then another one with progression of osteochondral
4 defect you can see on the right, on both sides of
5 the joint; and again, severe osteolysis on both
6 sides of the joint, with fragmentation of the
7 femoral head; and the final one, I think, again,
8 with quite severe impaction of the bone.

9 So the films were good enough to adjudicate
10 for these severe outcomes, and we progressed in
11 that manner. So we had 492 cases to review, 149
12 cases with no x-rays and no pathology. Therefore,
13 we did not adjudicate these 353 cases remaining for
14 review and adjudication. And of some of those, we
15 additionally found ones that could not be
16 adjudicated for various reasons.

17 So in this slide, I think the important
18 thing is the information at the bottom. In those
19 353, there were 288 individuals with one evaluable
20 joint and evaluable data so that the films were of
21 decent enough quality to read.

22 Among these 288, there were 80 patients with

1 high suspicion for a non-OA process in at least one
2 joint. Of those, 72 had one joint with what we
3 thought was a non-OA process and 8 patients in whom
4 there were two joints that we thought had high
5 suspicion for a non-OA process.

6 So of these 288, 285 were known in terms of
7 their treatment allocation. So the following
8 slides, then, focus on either, in the evaluable
9 patients, those who had a high suspicion lesion for
10 a non-OA and those who did not have a high
11 suspicion lesion for non-OA but were still
12 adjudicable.

13 So our initial evaluation was outcome by
14 treatment allocation. And you see, in the anti-NGF
15 group, we're combining all three agents. There was
16 about a twofold numerical increase in prevalence of
17 high suspicion lesions. This did not quite meet
18 statistical significance.

19 When we looked at outcome, high suspicion
20 lesion versus no high suspicion lesion, by
21 individual drug allocation, there was a
22 statistically significantly higher prevalence of

1 high suspicion lesions in the tanezumab group
2 compared to placebo. And again, we lumped the
3 placebo groups from various studies, so you could
4 take issue with that. We did not see a
5 statistically significant increase in the
6 prevalence of these lesions with the other two
7 drugs. Whether this is a true finding or a
8 manifestation of lower numbers of patients is not
9 known.

10 We then look at the outcome as a function of
11 treatment allocation with and without concomitant
12 NSAIDs that they received as part of the
13 randomization procedure. And I did appreciate the
14 comment that was made this morning about potential
15 misclassification of patients in the low back pain
16 studies with fulranumab. And we will take that
17 into account. I don't know for sure how we
18 adjudicated that.

19 But here, we see, according to the
20 adjudication as shown, that when we look at
21 treatment with anti-NGF without NSAIDs, there is no
22 statistical increase in high suspicion lesions in

1 that group compared to placebo. However, there is
2 a statistically significant increase in prevalence
3 of these lesions in the anti-NGF group with NSAIDs
4 compared to both placebo and compared to the
5 anti-NGF group without NSAIDs.

6 When we look at tanezumab individually,
7 because it had the highest number of events, again
8 we do not see an increased prevalence of high
9 suspicion lesions in tanezumab without NSAIDs
10 compared to placebo, but we do see a significant
11 increase in tanezumab with NSAIDs, both compared to
12 placebo and tanezumab without NSAIDs.

13 So then, going to our second outcome, which
14 is the change in joint, so marked deterioration or
15 not, there is a statistically significant increase
16 in the incidence of marked deterioration in the
17 group receiving anti-NGF therapy compared to
18 placebo.

19 When we look at this outcome of
20 deterioration by anti-NGF therapy with and without
21 NSAIDs, you can see that there is a statistically
22 significantly increased incidence of deterioration

1 in the anti-NGF group without NSAIDs compared to
2 placebo. There's also an increased incidence in
3 anti-NGF with NSAIDs compared to placebo, but there
4 was no difference in incidence in the two anti-NGF
5 groups themselves.

6 We did not look at individual drugs with
7 this because the number is smaller than in the
8 cross-sectional data analyses.

9 So a summary to this point is that in the
10 pre-surgical time point, looking at the state of
11 the joint pre-surgically, there was borderline
12 significant association between anti-NGF treatment
13 and a non-OA process. And again, by non-OA
14 process, we mean a bad outcome involving a lot of
15 bone damage. Anti-NGF treatment plus NSAIDs was
16 significantly associated with non-OA process
17 compared to placebo with or without NSAIDs and
18 compared to anti-NGF without NSAIDs.

19 In terms of the change in the joint during
20 the study, there was marked deterioration
21 significantly associated with anti-NGF therapy, and
22 the incidence of marked deterioration was not

1 significantly higher in the anti-NGF plus NSAIDs
2 group, compared to anti-NGF alone.

3 We then looked at the sponsors'
4 adjudication, just analyzing the data in a similar
5 way. And as you've already heard, the way that the
6 sponsors adjudicated their data were relatively
7 similar in terms of choosing rapidly progressive,
8 normal progressive, indeterminate, and then other
9 or no consensus.

10 One thing to point out is that, as far as I
11 can determine from the adjudications, the term
12 "progression" was used in many cases where there
13 was not a pre-study film, and it was based on the
14 appearance of the joint at that pre-surgical time
15 point.

16 So I'm going to focus on the analyses with
17 the sponsors by combining the primary ON with
18 rapidly progressive OA as the bad outcome. And
19 normal progression is normal progression.

20 So if we look at the outcomes for the
21 sponsors' adjudication similar to the way that we
22 did it and divide the patients by either

1 osteonecrosis combined with RPOA versus no ON or
2 RPOA, anti-NGF therapy was associated with a
3 significant increase in those outcomes compared to
4 placebo.

5 If we look at the outcome by a specific drug
6 allocation, again, we see a significant increase in
7 any osteonecrosis or RPOA in the tanezumab group
8 compared to placebo, as well as the fulranumab
9 group compared to placebo.

10 If we look at outcome by treatment with or
11 without NSAIDs, anti-NGF without NSAIDs showed a
12 significant increase compared to placebo in terms
13 of these poor outcomes. Anti-NGF with NSAIDs was
14 significantly higher in terms of placebo, but not
15 compared to anti-NGF without NSAIDs for these
16 outcomes.

17 If we then look at tanezumab specifically,
18 again using this same analysis scheme, tanezumab
19 without NSAIDs had a higher prevalence of ON or
20 RPOA compared to placebo, as did tanezumab with
21 NSAIDs. But there was no significant difference
22 between the two tanezumab groups.

1 So a summary in terms of analysis of the
2 sponsors' adjudication results in an attempt to
3 look at them in a consistency in the way we
4 analyzed our data, we saw a significant association
5 between poor outcome in the anti-NGF group compared
6 to placebo and that the combination of anti-NGF
7 therapy with NSAIDs, whether analyzed as a group or
8 as tanezumab only, was not associated with a higher
9 rate of adverse outcomes than anti-NGF without
10 NSAIDs.

11 We were asked by the FDA to compare our
12 adjudication results with the sponsors', and that's
13 why we ran through that prior analysis of the
14 sponsors' data by our analysis scheme. The caveats
15 here are that the sponsors' adjudication committees
16 again had the original images and slides, and we
17 did not. And again, our outcomes were different.
18 But we considered in our outcome, that we called
19 the state of the joint -- we considered that our
20 categories of high suspicion for non-OA process and
21 the sponsors' committee categories of ON and RPOA
22 were potentially concordant, so that's how we

1 approached the data that you'll see subsequent to
2 this slide.

3 As for the change in the joint, we could not
4 compare our data to the sponsors', since they did
5 not, that I could tell, distinguish the state of
6 the joint from a change in the joint. And again,
7 as I mentioned, the sponsors' adjudication
8 committees used the term "progression" regardless
9 of whether there was a pre-study film or not, I
10 think. I could be corrected on that.

11 So these are our rates of concordance. So
12 where the sponsors' outcome was no osteonecrosis or
13 rapidly progressive OA and the Columbia outcome was
14 no high suspicion for a non-OA process, this
15 represented 65 percent of the patients analyzed.

16 If we look at the bottom of the sponsors'
17 outcome, of ON or RPOA, and our outcome of high
18 suspicion for a non-OA process, this represented
19 22.5 percent of the patients. So you can see at
20 the bottom of the slide that concordance, then, was
21 present for almost 88 percent of patients,
22 representing 234 of the 288. And non-concordance

1 was present only in 12.4 percent. So we think that
2 we are looking and identifying the same processes,
3 even though we're calling them different names.

4 So then we ran an analysis where we took
5 only those for whom we had concordant adjudication,
6 and then we looked at our analyses in a similar
7 process, as I've already shown you.

8 So here we looked at outcome by treatment
9 assignment, and we're combining now the patients on
10 the top for whom there was no high suspicion for
11 ON/RPOA, or non-OA process. And then the bottom is
12 any high suspicion for ON/RPOA, or non-OA process.
13 And you can see that anti-NGF, by this analysis,
14 was associated with a higher prevalence of a poor
15 outcome, the p-value that was statistically
16 significant.

17 Here, we look at this outcome by treatment
18 with or without NSAIDs. And here, anti-NGF
19 treatment without NSAIDs did not have a higher
20 prevalence of poor outcomes compared to placebo,
21 whereas anti-NGF with NSAIDs did. And anti-NGF
22 with NSAIDs had a higher prevalence of adverse

1 outcomes compared to anti-NGF without NSAIDs.

2 If we then look specifically at tanezumab
3 again, because it has the higher number of events,
4 again you see no difference in prevalence of poor
5 outcomes with tanezumab without NSAIDs compared to
6 placebo, but there is a higher prevalence of these
7 poor outcomes in the tanezumab with-NSAID group
8 compared to placebo, but no statistically
9 significant difference between the two tanezumab
10 groups.

11 So a summary to this point is that we see
12 high rates of agreement for poor outcomes between
13 the sponsors' adjudication and ours, despite our
14 limited quality data. When the analyses are
15 restricted to participants with concordant
16 outcomes, anti-NGF therapy was associated with a
17 higher rate of the combined concordant outcomes
18 compared to placebo. A combination of anti-NGF
19 with NSAIDs was associated with a higher rate of
20 poor outcome in some of the analyses.

21 Now, we did some additional analyses with
22 the goal of identifying any imbalances in baseline

1 characteristics of participants that might
2 be -- when we analyzed the patients by outcomes, we
3 were interested in whether there were any
4 imbalances in baseline characteristics or some
5 variables that might have changed during the study,
6 such as the addition of NSAIDs.

7 So we wanted to look at these in multi-
8 variable analyses. We also were interested in
9 whether there might be a dose response in the
10 relationship of anti-NGF therapy to poor joint
11 outcomes. So first, we looked at baseline
12 characteristics according to outcome, whether it
13 was negative or positive. And this is going back,
14 again, to the Columbia adjudication, so outcome
15 positive was, in this case -- in the cross-
16 sectional analyses, it was marked bone changes, as
17 I've elucidated, or marked deterioration. So no
18 patient was counted twice. They either had a non-
19 OA process or a marked deterioration to. To be in
20 the outcome positive group and outcome negatives
21 were the others.

22 Mostly, they were balanced according to

1 outcome, except for a few exceptions. You can see
2 that there were more men in the outcome positive
3 group by percentage than in the outcome negative
4 group. Current smokers were higher by percentage
5 in the outcome positive group than the outcome
6 negative.

7 When we looked at history of prior trauma
8 before entering the study, there was actually a
9 higher percentage in the outcome negative group
10 than in the outcome positive group. Notice that
11 the KL scores did not differ at baseline between
12 the two groups.

13 As suggested already by the analyses that we
14 showed you, the NSAID use was higher in the outcome
15 positive group than the outcome negative. And
16 then, if you look at the last three lines, we broke
17 the anti-NGF therapy very grossly into some dosage
18 categories. Some of the studies had two phases
19 that could be placebo going to drug, I think, or
20 low dose possibly going to high-dose drug. So we
21 just broke them fairly grossly into either no
22 anti-NGF therapy in either phase, low dose in both

1 phases, or high dose in either or both.

2 Now, the description of the definition of
3 low dose and high dose was fairly gross, and
4 admittedly, one can't compare drug to drug,
5 milligram per milligram. But because the two
6 drugs, tanezumab and fulranumab, had similar doses,
7 we made a gross adjustment of greater than
8 9 milligrams as high dose and anything less than 9
9 milligrams was low dose. And we could not adjust
10 for duration of treatment exactly because we didn't
11 have all the data that we needed for that.

12 By this gross definition of high dose, low
13 dose, or no anti-NGF therapy, you can see that
14 there's a higher percentage of patients receiving
15 placebo-only in the outcome negative, a higher
16 percentage of folks receiving low dose in the
17 outcome negative group, and in the high dose, a
18 higher percentage in the outcome positive group.

19 So we look these factors and then went on to
20 do some multi-variable analyses, which I'll show
21 you in a second. We also looked at participant
22 characteristics according to treatment by those

1 definitions that I just used, no anti-NGF therapy,
2 low dose, or high dose.

3 We looked at baseline characteristics, and
4 there were no differences by this division or this
5 distribution according to age, gender, race, BMI,
6 alcohol intake, history of OA or ON going into this
7 study, history of trauma, baseline KL scores,
8 et cetera. The only differences that we saw were
9 smoking and the use of NSAIDs, as I've already
10 shown you.

11 So these are multi-variable analyses where
12 we looked at the association of anti-NGF dose with
13 high suspicion non-OA or rapid deterioration, so
14 the cross-sectional or the progression study.
15 Model 1 represents unadjusted odds ratios for the
16 effective low dose and high dose relevant to
17 placebo, effect for causing or being associated
18 with these bad outcomes.

19 Model 2 takes the variables that were
20 discordant or not balanced between the two groups
21 at baseline. And if you look at the unadjusted
22 values, you see that with low dose, the odds ratio

1 of having one of these bad outcomes was fourfold
2 higher than the reference group. And for high
3 dose, it was eightfold higher. And the confidence
4 intervals are shown there.

5 Model 2 is the adjusted values, and you can
6 see fairly high odds ratios for each of the doses
7 being associated with these poor outcomes. Both of
8 them are statistically significant. Because the
9 confidence intervals are quite wide, I wanted to
10 show you the actual frequencies, unadjusted and
11 adjusted, here.

12 We then looked at these outcomes in
13 association with anti-NGF dose plus or minus
14 analgesics. And here, since we have the narcotics
15 data, we put those together with the NSAIDs data.
16 And again, we're mixing and matching study to study
17 and drug to drug, which has its limitations,
18 obviously.

19 We included the analgesics, both NSAIDs and
20 narcotics, because of this issue about whether one
21 could cause a Charcot-like joint with one, two, and
22 three medications that could limit pain. So what

1 you see here is the placebo again. Model 1, again,
2 is unadjusted. Model 2 is adjusted. And we have
3 four groups: low dose with no analgesics, low dose
4 with analgesics, high dose with no analgesics, and
5 high dose with analgesics.

6 What you see, if we just go right to the
7 adjusted models, model 2, that low dose without
8 analgesics does not result in a significant
9 increase in the odds ratio for having a bad
10 outcome. Low-dose NGF plus analgesics and high-
11 dose anti-NGF with no analgesics both raise the
12 odds ratio for having a bad outcome, and both of
13 these are statistically significant. High dose
14 plus analgesics raises the odds ratio even further,
15 again statistically significant. And again,
16 because these confidence intervals and odds ratios
17 are quite high and wide, I'm showing you the
18 frequencies here, both unadjusted and adjusted.

19 We then looked at our data just for joint
20 deterioration, taking out the cross-sectional
21 analyses and just looking at those patients who had
22 deterioration. And with the adjusted model,

1 model 2, you can see that the number goes down even
2 more because we didn't have data on all of these
3 factors that we wanted to adjust for, so we were
4 left with a model of only 101 patients. And what
5 you see here is, in model 2, that high dose was
6 associated with an increased odds ratio for having
7 a bad outcome. And again, I show you the
8 frequencies here, unadjusted and adjusted.

9 Lastly, we analyzed the outcome as a
10 function of low dose/high dose, with and without
11 analgesics according to the same format that I
12 showed you before. And if we move just to model 2,
13 again, you can see that the odds ratio for having a
14 poor outcome, again, deterioration is increased in
15 the three lower groups, low dose with analgesics,
16 high dose with and without analgesics, all of which
17 the last two, are statistically significant. And
18 here again are the frequencies.

19 So the conclusion at this stage is that the
20 relationship of anti-NGF therapy with poor joint
21 outcomes persists even after adjustment for some
22 baseline imbalances and potential confounders, that

1 a dose-responsive anti-NGF therapy with odds of
2 having a poor outcome is suggested by the data.
3 But I did not present what we saw in our analyses
4 were similar results when we analyzed in a similar
5 way with using this sponsors' adjudication
6 outcomes.

7 So limitations, I've already pointed out.
8 It's that our source data was suboptimal, but we
9 did limit our outcomes to dramatic joint changes.
10 We also didn't have the full denominator, the total
11 number treated, to fully understand the risk. But
12 we did have a sufficient number of placebo-treated
13 patients to provide a risk estimate.

14 We're not going to go into causes because
15 that's a subject for discussion, but I do want to
16 direct your attention to point number 3. We got an
17 impression -- and to really know this, we'd have to
18 go back and look at every patient again
19 individually. There were quite a few -- and I
20 can't give you numbers, so take it with a grain of
21 salt. But there were quite a few reports of tendon
22 ruptures during the trial. And we wondered in some

1 of these patients that had severe subluxation, if
2 that problem was contributing to some of the
3 deformity as well. But clearly, there was a lot of
4 bone degradation.

5 The other qualitative comment I want to make
6 is that we saw a lot of osteochondral defects in
7 the plain films. And when we went back through the
8 Pfizer adjudications, where there was a nice
9 description of each of the cases, it seemed that
10 most of the osteochondral defects that we had
11 identified, or at least many of them, correlated
12 with what was seen on the MRIs in sufficiency
13 fractures.

14 So that's it. Thank you.

15 **Clarifying Questions to the FDA and Speaker**

16 DR. BUCKLEY: We will start with questions
17 for Dr. Bathon, maybe, while you're up. You want
18 to stay for a minute? And then we'll broaden it
19 out to questions to the FDA, and we'll start to
20 take a show of hands.

21 While we're waiting, Dr. Bathon, can I ask
22 you a question about the data you just presented?

1 So it suggests that if the patients were on an
2 anti-NGF and an analgesic, they were more at risk.

3 DR. BATHON: Yes. It wasn't always
4 consistent, depending on the numbers of patients
5 and how the analyses were done, but that was the
6 flavor. It wasn't absolutely consistent from
7 analysis to analysis.

8 DR. BUCKLEY: Yet, when you look at the
9 data, it looks like when the patients were rating
10 their pain level when they were on the combination,
11 they weren't rating their analgesia. In other
12 words, those on a combination of, for example
13 NSAIDs and an anti-NGF, weren't necessarily rating
14 their pain. It didn't look like it was a more
15 effective combination in terms of pain.

16 DR. BATHON: Yes. We did not analyze -- we
17 definitely saw -- when we looked at the WOMAC
18 changes in pain from pre- and post-, it did seem
19 like patients who were on anti-NGF had more pain
20 relief, as already presented. It didn't seem to
21 correlate necessarily with the outcomes, though.

22 DR. BUCKLEY: Okay.

1 Next question from Dr. Khurana?

2 DR. KHURANA: So one of the things we're
3 supposed to talk about, I guess topics for
4 discussion, is whether osteonecrosis does or does
5 not present a safety signal. And there's obviously
6 a big difference in the amount of osteonecrosis
7 between the sponsors and the review by the FDA.

8 So the question really is for Dr. Colburn.
9 There was a big difference between the numbers of
10 osteonecrosis seen in her review, as compared to
11 the sponsors' review. Why the difference? And was
12 the pathology reviewed? Because that was supposed
13 to be the gold standard in your study. So a lot of
14 cases were changed to osteonecrosis.

15 DR. COLBURN: Yes. That's a very good
16 question because I hope I brought that out during
17 my presentation, is that I really considered the
18 diagnosis of osteonecrosis in a literal and
19 de facto sense. In other words, if I had
20 characteristic pathology slides and/or
21 readings -- because I did have readings available
22 to me -- and/or I had characteristic radiographs or

1 MRIs, either to look at and/or to review the
2 radiologist's reading, I gave the diagnosis of
3 osteonecrosis.

4 DR. KHURANA: I'm sorry. Maybe I wasn't
5 clear. But the discrepant cases, where they found
6 no osteonecrosis, was the pathology reviewed?

7 DR. COLBURN: Yes. They reviewed pathology
8 as well. The difference that you're seeing is
9 really how we're interpreting, how I'm
10 interpreting, how the sponsors are interpreting the
11 diagnosis of osteonecrosis. That's where you're
12 seeing the difference. Because, although when I
13 was reading the sponsors' review of cases that had
14 been designated as osteonecrosis, there was a lot
15 of discussion as to why there would be dead bone,
16 as to why the x-ray would look this particular way,
17 as to why -- a lot of their adjudication actually
18 ended up summarizing that the radiology report was
19 incorrect, that this was not osteonecrosis.

20 But again, I have to emphasize that in my
21 clinical judgment and insight, as I looked at these
22 radiology, either the reports, the images, and the

1 pathology, either the slide images or the reports,
2 if there was evidence for dead bone, the diagnosis
3 was osteonecrosis.

4 Now, you'll note that I go further to say
5 that there is a primary and secondary
6 differentiation of osteonecrosis. Okay? So if
7 you'll note, Pfizer only mentions osteonecrosis in
8 their adjudication categories as a primary
9 osteonecrosis. But when I regard the
10 relatedness -- so I guess what the confusion may be
11 here is that there's two different processes that I
12 underwent in making a clinical judgment.

13 First, I categorized each case or each joint
14 into the adjudication category -- okay -- based on
15 what I had set forth in my adjudication summary as
16 to how I would classify these. Then at the end,
17 once I obtained under that adjudication category
18 where the joint would be replaced, I was then asked
19 to make a decision as to whether I felt that would
20 possibly be drug related or not.

21 Now, in the case of osteonecrosis, as you
22 know, there's primary and secondary. And of course

1 you know that any secondary osteonecrosis would be
2 the possibility of drug-relatedness. But our
3 sponsor really does not discuss that. When they
4 talk about osteonecrosis, they only talk about
5 primary osteonecrosis.

6 Certainly, I saw some primary osteonecrosis.
7 I saw cases of Freiberg's. I saw cases of
8 congenital hip dysplasia that had been probably
9 read, and the safety signal picked up at that time
10 as osteonecrosis.

11 So in making the diagnosis, I put that under
12 the adjudicated category of osteonecrosis. But in
13 making the decision as to relatedness, if I felt
14 that that was truly primary osteonecrosis,
15 idiopathic, not secondary to any defined,
16 underlying etiology, I considered that secondary
17 osteonecrosis and possibly relatedness.

18 DR. KHURANA: Yes. I apologize. I know we
19 have to move on and not spend all the time on one
20 topic, but I just wanted to confirm that the slides
21 were actually reviewed, the glass slides were
22 reviewed, not just images and reports.

1 DR. COLBURN: The actual slides? No. No.
2 I didn't have actual pathology slides, so I had
3 digital imaging of pathology.

4 DR. BUCKLEY: Next question from Dr. Neaton?

5 DR. NEATON: I just want to, first of all,
6 clarify. Your presentation of the data is very
7 different from what we heard earlier from the FDA
8 and the sponsors. Your denominator is essentially
9 people that had joint replacements or
10 osteonecrosis.

11 DR. BATHON: Correct.

12 DR. NEATON: So when you studied factors
13 related to progressive ROA, then basically it was
14 like taking all-cause mortality and asking the
15 question, is there a difference between people who
16 died from heart attacks versus accidents.

17 DR. BATHON: Yes.

18 DR. NEATON: You have left out everybody in
19 your analysis that didn't have a joint replacement
20 or a diagnosis of osteonecrosis.

21 DR. BATHON: And it turned out that -- yes,
22 I mean, I agree. Ninety-nine percent of the

1 patients in our group had OA, so it was a non-
2 issue, actually.

3 DR. NEATON: Yes. That's why --

4 DR. BATHON: They were apples and apples in
5 that regard.

6 DR. NEATON: I think it's important for us
7 to understand that. I come back to my question
8 earlier this morning for the FDA, which I think you
9 began to address it in one of your slides. But it
10 seems like what we need to see and be comfortable
11 with are the joint replacements and the progression
12 of OA -- and it sounds like the adjudication,
13 whether you did it, or the FDA, or the sponsors, is
14 reasonably similar, so I don't care which one we
15 use -- by treatment group; so where the placebo
16 comparisons are done with the trials that use
17 placebo, and the combination comparisons are done
18 in the trials that use combination, and not just
19 lumped together.

20 That's kind of what's missing right now in
21 my mind, both from the FDA and the sponsors'
22 presentation. And once we have that, then I think

1 you can use all the data, which I think is very
2 important. The sponsor has indicated in their
3 reports the preliminary analyses, but it seems like
4 a lot more could be done to understand risk factors
5 for people who develop the progressive ROA, now
6 that you have the adjudicated diagnoses.

7 So I guess I'll pose it as a question. Does
8 the FDA have that information?

9 DR. COLBURN: Can I address that?

10 Yes. I think that is an excellent point, in
11 making that comparator to the placebo groups. And
12 I think I touched upon that. But, please, I was
13 really limited in my statistics to none, because
14 really what I did in my presentation was more of a
15 descriptive and categorical analyses, where I did
16 talk and say, you know, here's a table. Here's the
17 greater number in these treatment groups. Here's
18 the zeros across the placebo group. But you're
19 right. That needs a statistical analyses.

20 DR. NEATON: I have maybe a follow-up
21 question. I'm understanding, from your conclusion
22 side, from the FDA, that you think that for joint

1 replacements, there's not much difference between
2 monotherapy and placebo. However, for progression
3 of OA, there is a difference. That's kind of my --

4 DR. HERTZ: So we have some backup slides
5 that might lend a little clarity.

6 DR. COLBURN: No. They don't have them as
7 slides.

8 DR. HERTZ: Oh. I can describe them to you
9 verbally.

10 So for instance, if you just look at -- and
11 Pfizer might have some of this. This is based on
12 tanezumab materials that you guys sent us. But if
13 you look at the incidence of sponsor-adjudicated ON
14 and RPOA in tanezumab placebo-controlled OA trials
15 only -- so it's eight studies, okay -- there
16 were --

17 DR. NEATON: According to my count for
18 Pfizer, there were six studies, and two they
19 eliminated because they were stopped.

20 Is that correct?

21 DR. HERTZ: Well, this is with eight
22 studies. So needless to say, the data was sliced

1 and diced quite a few ways just to look at all of
2 the available information and from many different
3 perspectives.

4 But there were very few cases in this set of
5 data. So there were approximately 1,000 placebo,
6 2500 tanezumab, 575 active comparators. There were
7 only three cases, so compared to nothing and
8 nothing. So it was very few in that cluster of
9 studies.

10 DR. NEATON: That's kind of what I wanted to
11 get at because one conclusion is, concerning the
12 monotherapy, it just doesn't have any power.

13 DR. HERTZ: Right.

14 DR. NEATON: So stating that there's no
15 differences is a lot different than saying we just
16 don't know. And so, that's what I don't
17 understand.

18 DR. VERBURG: Since it's the Q&A session for
19 the FDA presentation -- but we can take you through
20 each component, I think, that you've asked us for.
21 And Dr. Hertz did a nice job of actually describing
22 it. I think you'll find that, if you want to look

1 at, strictly speaking, a placebo comparison for
2 rapidly progressive OA, as she mentioned, there's
3 only three events in the entire cohort of those
4 studies, so you can't make a comparison. When it
5 comes to all-cause total joint replacements, you
6 can't. And we can take you through basically how
7 we built the slides that I showed, wherein
8 components of placebo-controlled trials, active-
9 controlled trials, 1025 alone, and the long-term
10 non-controlled trials, either NSAID, combined, or
11 patients split into NSAID users, and not. And I
12 think you'll see that situation hangs together
13 pretty well and allows us to make and build the
14 story. But I can understand you wanting to see a
15 clear line of sight to that. But we could do that
16 later if the committee would like.

17 DR. BUCKLEY: I think we will move on to the
18 next question. Dr. Neogi?

19 DR. NEOGI: This question is for Dr. Colburn
20 or the sponsors. There is mention of subchondral
21 insufficiency fracture. And I just wanted to know
22 what was that on imaging. And on MRI, is that

1 different than the subchondral bone attrition seen
2 in osteoarthritis?

3 DR. COLBURN: Yes. That's a great question.
4 So in this -- when I saw these things, because of
5 the poor quality again of digital imaging and the
6 fact that I am not a musculoskeletal radiologist, I
7 depended to say that there was subchondral
8 insufficiency fractures based on the true
9 professional. And that's the radiologist who gave
10 that reading or interpretation.

11 So if that was there, and I felt like that
12 was a major part of the clinical presentation, then
13 I would adjudicate that as something like other,
14 subchondral insufficiency fracture. If, however,
15 there was subchondral insufficiency fracture
16 together with other pathognomonic imaging criteria
17 for osteonecrosis, I really adjudicated that as
18 osteonecrosis.

19 DR. BUCKLEY: Dr. Lahita?

20 DR. LAHITA: That was in line with what I
21 was going to ask. There's a fair amount of basic
22 science literature about nerve growth factor and

1 angiogenesis, and neovascularization. I have two
2 basic science papers here in front of me.

3 My question to Dr. Bathon would be, in the
4 plain films, osteochondral defects seen by the
5 Columbia radiologist, as well as the question just
6 asked about subchondral insufficiency fractures, is
7 that consistent with osteonecrosis? And I think
8 you answered that. And based on inhibition of the
9 nerve growth factor inducing ischemia locally,
10 would that be a plausible hypothesis?

11 DR. COLBURN: Yes. As a matter of fact, in
12 using my clinical judgment, just as a clinician,
13 when you start to see repeating patterns over, and
14 over, and over, you start to get an idea. I really
15 think, in my clinical judgment, that probably the
16 first thing -- and this may be the chicken or the
17 egg thing. But I think the first thing that may
18 have occurred in this setting was that NGF is there
19 locally, is starting to break down in the
20 protective sensory input, and that the bone is
21 actually responding to this. It's probably
22 starting to break down. And the first breakdown

1 possibly are these subchondral insufficiency
2 fractures, which then is escalated, probably --
3 whatever environmental, milieu, whatever genetic
4 predisposing factor there may be for bony
5 destruction, you just start to get either one of
6 these clinical types of pictures. You get an
7 osteonecrotic picture, where then bone then starts
8 to die. Maybe it dies slower. You get collapse of
9 the bone, or you get this rapid destruction of the
10 bone.

11 So that's just my two cents.

12 DR. LAHITA: Let me just explain on that and
13 just say, with regard to NSAIDs, from the
14 pathologists' point of view, we know that NSAIDs
15 cause vasoconstriction in other parts of the body.
16 Is there any evidence that, that happens at the
17 level of the synovium, at the joint level, that we
18 get vasoconstrictive, such as in this hip, this
19 NSAID hip, or anti-inflammatory hip, or whatever it
20 was called when it was presented?

21 In other words, would there then be a
22 cumulative effect, inhibition of NGF, and

1 vasoconstriction from the NSAID?

2 DR. COLBURN: No. I guess I'm not a true
3 expert. Again, I have a lot of history of doing
4 basic science studies, having worked over at NIH
5 and everything. And so when I think about these
6 things, certainly, neogenesis. We know one
7 osteonecrosis -- one of the underlying
8 pathophysiology of osteonecrosis has always been
9 felt to be some vascular insults, some vascular
10 insufficiency. So you could potentially tie those
11 things together.

12 Do I have evidence for that? Certainly not,
13 certainly not. But just again, as a clinician who
14 sees kind of a repeating pattern, these are just
15 some thoughts that I have.

16 DR. BUCKLEY: So we have about 10 or
17 15 minutes and a number of questions, so just two
18 reminders. One is that, I'd like as much as we
19 can, so we can get everyone in, a quick, pointed
20 question, and probably we'll only take one
21 question. And second is, again, to state your name
22 because it's being recorded.

1 So the next question is from Dr. Mikuls.

2 DR. MIKULS: I had two questions, but I
3 guess I'll whittle it to one after that rebuke. I
4 think my most important question for the FDA -- and
5 whoever wants to jump at it can -- is, some of the
6 most important data I think that was presented by
7 the sponsors was in terms of risk mitigation.

8 Did the FDA have an opportunity to repeat
9 that exam with the cases that were adjudicated in
10 terms of the ability to mitigate risk?

11 DR. HERTZ: This is Dr. Hertz from FDA. No,
12 we didn't do that.

13 DR. BUCKLEY: Dr. Kelly?

14 DR. KELLY: Yes. I just want make a comment
15 and then a question. As a knee surgeon, I don't
16 see that much RPOA, so it's just a little
17 surprising to see this. However, I want to echo
18 what Dr. Neaton said.

19 To take a total joint population and work
20 backwards, there's so much subjective bias. It's a
21 very subjective, personal decision. And to make
22 these conclusions based on total joint

1 replacements, to me, is an extreme bias that's
2 introduced into all these studies. It'd be much
3 more meaningful, as Dr. Neaton recommended, to
4 follow Kellgren's scores longitudinally and to
5 determine rate progression objectively.

6 The second point that I have to make is that
7 we look at total joint replacements in a subluxed
8 and a fragmented joint. That's a different animal
9 than just a diffusely worn-out joint, so that has
10 to be taken into consideration, too. Just because
11 they had total joints didn't mean that the
12 operation was any easier or harder, from the data
13 we have.

14 DR. COLBURN: May I make a comment?

15 Yes. I'd like to comment that I did read
16 the operative reports, and that was part of the
17 narrative of the history and the physical. And I
18 would like to comment that in reading those reports
19 from the orthopedic surgeons, this clearly was an
20 entity that they were impressed by. They were
21 seeing this joint several months or maybe a year
22 prior. They're now seeing this joint with an acute

1 need, basically, for a joint replacement.

2 Some had advanced to the point where it
3 took -- and I can think of two to three instances
4 just off the top of my head where it took a
5 complicated primary joint. In other words, there
6 had to be particular structuring of the bone in
7 order to get the proper prosthesis to fit. And so
8 these ended up being difficult primary cases.

9 DR. KELLY: I just want to make the point
10 that that endpoint of total joint replacements is
11 flawed on both ends --

12 DR. COLBURN: Yes.

13 DR. KELLY: -- in deducing outcomes. And
14 also, there's joints and there's joints. So thank
15 you.

16 DR. BUCKLEY: Dr. Boyce?

17 DR. BOYCE: My question is to Dr. Bathon
18 about the review of osteonecrosis cases. Did you
19 find similar differences that Dr. Colburn found in
20 the review of the pathology?

21 DR. BATHON: So we couldn't really
22 adjudicate osteonecrosis very well, and that's why

1 we actually did not adjudicate on it. We just
2 called a non-OA a high suspicion for a non-OA
3 process. We used the pathology, but it was only
4 useful as -- we used it as a gold standard if there
5 was osteonecrosis.

6 But in terms of primary osteonecrosis, where
7 that was the only finding, that was rare, usually
8 it was seen in conjunction with osteoarthritis, or
9 fracture, or fragmentation, and so forth. So if it
10 was seen in the context of all those other things,
11 we called it a non-OA outcome.

12 DR. BOYCE: So did you agree, then, with the
13 sponsors and their interpretation?

14 DR. BATHON: I'm sorry. What was the
15 question?

16 DR. BOYCE: Did you agree with the sponsors
17 and their interpretation, or did you agree more
18 with Dr. Colburn and her interpretation?

19 DR. BATHON: I think it's so hard to tell
20 because we all took all aspects into consideration
21 for our final adjudication. So it wasn't just
22 a -- I think the images were the primary driver. I

1 don't think I know -- the images were the primary
2 driver in how we adjudicated. The pathology was
3 used in most cases to confirm, but rarely to
4 refute.

5 DR. BOYCE: You didn't see the glass slides?
6 It was digital images or something?

7 DR. BATHON: No. And I thought other folks
8 had them, but I guess -- yes, we just had

9 DR. BOYCE: It's really very important to be
10 able to see these glass slides to be able to make
11 an appropriate interpretation and to be sure that
12 the material has been taken from the appropriate
13 parts of the joint or the specimen.

14 DR. BATHON: And that was what our
15 pathologist emphasized, as we didn't know where
16 they were sectioned from, whether it was from the
17 OA area or the suspected infarct area. And that's
18 why we couldn't say with any assurance that there
19 was no ON. We could only say when there was ON.

20 DR. BUCKLEY: Next question from Dr. Haque?

21 DR. HAQUE: I have one comment. Mustafa
22 Haque. I have one comment and one question.

1 Hopefully we can ask some more questions later.
2 But I agree with Dr. Kelly in his comment, that the
3 rapidly progressive osteoarthritis is a relatively
4 rare finding. I mean, I've been doing orthopedics
5 for about 15 years; now, becoming the upper
6 extremity. And I also did a JBJS literature
7 search, which is our primary orthopedic journal,
8 and did not find a single article on rapidly
9 progressive osteoarthritis. So the thought that
10 that's 1 in 6 cases of arthritis is a little bit
11 strange to me.

12 My main question, though, right now for
13 Dr. Bathon is, from the data from the tanezumab
14 work, there were 87 people who were identified with
15 osteonecrosis, but only 50 went on to total joint
16 replacement to date or at the time of the analysis.
17 So there's 37 still pending. And I'm just
18 wondering whether or not those people are included
19 in the total joint data. How is that data parsed?

20 I mean, that's a fairly high percentage of
21 these people. Where do they fall as far as the
22 analysis?

1 DR. BATHON: At some point -- and the
2 sponsors could comment on this better than I. But
3 at some point, when there was concern, as I
4 understand it, patients -- there was built into
5 some of the studies that they had bilateral
6 shoulder and hip films. And some of these cases
7 were picked up by these routine x-rays as well that
8 didn't yet have surgery. But maybe you could
9 clarify that.

10 DR. BUCKLEY: I think we'll hold on the
11 sponsors' response for this unless it's very quick.

12 DR. BATHON: Sorry.

13 DR. VERBURG: Yes. It is. I was just going
14 to ask the FDA if they knew for sure if they had
15 taken our 386 cases or case sets, and sent them to
16 Dr. Bathon, and she had those cases that were
17 osteonecrosis, but not associated with a total
18 joint replacement yet.

19 DR. HERTZ: Yes. I did.

20 DR. VERBURG: That's right? Then they were
21 part of the adjudication set.

22 DR. BUCKLEY: Next question, Dr. Cowan?

1 Ms. Cowan. Sorry.

2 MS. COWAN: Yes. Penny Cowan. And I was
3 just wondering, was there any kind of a follow-up
4 provided to the FDA? In other words, after the
5 surgery or after the medications were stopped, was
6 there any follow-up of the folks at all to see if
7 the deterioration, the osteonecrosis, has stopped
8 at all? Was there any of that?

9 DR. HERTZ: Dr. Hertz. We don't have that
10 information.

11 DR. COLBURN: Yes. I was going to say that
12 really my adjudication stopped pretty much at the
13 time of event, and that there were some who were
14 reported to have either RPOA or ON who
15 elected -- although, given the orthopedic consult
16 notes, who were strongly suggested to have total
17 joint replacement, there were a couple that I can
18 recall who elected not to undergo operative
19 intervention at that time.

20 DR. BUCKLEY: Dr. Suarez?

21 DR. SUAREZ-ALMAZOR: Maria Suarez-Almazor.
22 I had a general question either for the FDA or the

1 sponsors. I'm assuming that because these were
2 trials of osteoarthritis, all patients must have
3 had a baseline radiograph of the affected joint
4 just for inclusion criteria purposes. And I'm
5 wondering if any of the 17 trials had as a
6 criterion or as an outcome measure follow-up
7 radiographs at the end of the trial or the four
8 months later that you continued follow-up. And if
9 so, whether that was analyzed for any of the
10 trials.

11 DR. VERBURG: The answer is yes -- well, no
12 and yes. Your first question was, did patients
13 have to have a baseline radiograph before entering
14 the osteoarthritis trials, and the answer is yes.
15 But that baseline x-ray could have been within nine
16 months of actually entering the trial. And it was
17 of just the index joint, which was the joint under
18 study.

19 So it wasn't a complete work-up in terms of
20 a radiological profile if the patient's
21 osteoarthritis, if it affected multiple joints. So
22 there wasn't a protocol-driven x-ray that needed to

1 be taken within two weeks of entering the trial.
2 It could extend must longer.

3 The second thing is with regard to did we do
4 systemic radiographs. The answer is yes. In one
5 of our large studies, study 1025, we had intended
6 to do baseline and one-year serial radiographs of
7 either the hip or the index knee. That objective
8 got a little bit interrupted by the clinical hold,
9 but again, we can share that information later this
10 afternoon if you'd like.

11 DR. BUCKLEY: So the last question for this
12 session -- and we'll move the other questioners on
13 to later in the discussions; so we'll get back to
14 it -- is Dr. Gerstenfeld.

15 DR. GERSTENFELD: Gerstenfeld from Boston
16 University. I had two related questions. The
17 first comes back to the index joint and the
18 difference between the pathology, the failed joint,
19 and the index joint, and whether that had been
20 assessed in either one of the adjudications that
21 had been carried out to see what that difference is
22 and whether there was joint specificity to failure.

1 Then the second question for later
2 consideration, I guess, is even given the reduction
3 of therapeutic dosing and removal of NSAID, whether
4 there would be some determination of long-term
5 progression to failure, since these joints fail
6 over time, whether there'd be some attempt to
7 determine whether there was earlier general failure
8 of those patients that entered into longer-term
9 therapy with the drug.

10 Those are my two questions.

11 DR. COLBURN: I will answer the first part
12 regarding the pathology. So pathology was sparse.
13 There were slides. I think the sponsors maybe have
14 actually gotten glass slides so that they could
15 look at it and had a pathologist to look at it.

16 What I had was digital imaging. Now, in
17 order to get pathology, of course, there had to be
18 a surgery. Now, there were several cases where
19 there was diagnosis of RPOA, or ON, or whatever,
20 the ongoing diagnosis, and clinical management plan
21 that was evolving at that time, that did not have
22 pathology.

1 So the answer to that question is whether
2 they're related to the index joint or some non-
3 index joint. Pathology is sparse, so it's not a
4 lot of pathology out there to really look at.

5 Does that help pretty much address it?

6 DR. GERSTENFELD: I guess so.

7 DR. VERBURG: Yes. I would just like to add
8 to that. I mean, when we speak of the index joint,
9 we're speaking of the most symptomatic joint
10 identified by the patient prior to entry. Right?

11 Okay. I just wanted to make sure we have
12 that clarified.

13 Yes. After that, it's really difficult to
14 make an assessment based on pathology; was there
15 any differences between a patient whose joint
16 progressed to total joint replacement, as to
17 whether or not it was pre-identified by the patient
18 as being the most symptomatic and sort of
19 documenting any differences by pathology.

20 I think the second question you asked,
21 though, I could address real quickly again.

22 DR. BUCKLEY: I'm trying to restrict these

1 answers just to the FDA for now, but we'll get back
2 to those questions later, and we're running a
3 little over. So I think we'll pause here and move
4 on to the next part.

5 DR. BATHON: I could just agree with what
6 was said previously about the pathology, that there
7 weren't enough to really compare index and surgical
8 with any degree of confidence.

9 **Open Public Hearing**

10 DR. BUCKLEY: With a deep breath and a short
11 pause, we're going to move on to the open public
12 hearing. Just as a reminder, all registered open
13 public hearing speakers should check in at the
14 registration desk and pick up your open public
15 hearing badge, for those of you who haven't. And
16 we're just going to start with some comments before
17 we start with the first speaker.

18 Both the Food and Drug Administration and
19 the public believe in a transparent process for
20 information gathering and decision making. To
21 ensure such transparency at the open public hearing
22 session of the advisory committee meeting, the FDA

1 believes that it's important to understand the
2 context of an individual's presentation.

3 For this reason, the FDA encourages you, the
4 open public hearing speaker, at the beginning of
5 your written or oral statement, to advise the
6 committee of any financial relationships you may
7 have with the sponsor, its product, and, if known,
8 its direct competitors. For example, this
9 financial information may include the sponsor's
10 payment of your travel, lodging, or other expenses
11 in connection with your attendance at this meeting.

12 Likewise, the FDA encourages you, at the
13 beginning of your statement, to advise the
14 committee if you do not have any financial
15 relationships. If you choose not to address this
16 issue of financial relationship at the beginning of
17 your statement, it will not preclude you from
18 speaking.

19 The FDA and this committee place great
20 importance in the open public hearing process. The
21 insights and comments provided can help the agency
22 and this committee in their consideration of the

1 issues before them.

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

10 So we'll move and ask speaker number 1 to
11 step up to the podium, introduce yourself.

12 DR. CAROME: Good afternoon. My name is
13 Dr. Michael Carome, deputy director of Public
14 Citizen's Health Research Group. I'm testifying on
15 behalf of myself and Dr. Sid Wolfe, the director of
16 our group. We have no financial conflicts of
17 interest.

18 We strongly urge the FDA to permanently
19 suspend the clinical development of these anti-NGF
20 agents for the treatment of pain because of the
21 dramatic safety signals seen in clinical studies of
22 these agents, demonstrating an unusually high

1 incidence of rapid joint destruction.

2 In particular, we note the following.

3 First, the occurrence of rapid joint damage with
4 all three anti-NGF agents likely represents a class
5 effect of these drugs. Second, data from tanezumab
6 shows that the risk of rapidly progressive
7 osteoarthritis, or OA, rises as the dose and
8 duration of exposure increases. While use of
9 NSAIDs further increases the risk, the same trends
10 and risks are apparent in subjects having tanezumab
11 alone.

12 Third, data for fulranumab also suggests a
13 possible dose-response with respect to the
14 incidence of joint replacement surgery in OA
15 patients.

16 Fourth, no adequately tested doses of
17 anti-NGF agents have failed to show a causal effect
18 relationship with these adverse events.

19 Fifth, the FDA, in its review of the
20 available data, noted the following. "There
21 appears to be a safety signal of rapid joint
22 destruction associated with both anti-NGF agent

1 monotherapy and anti-NGF agent plus NSAID therapy.
2 The incidence of this event is more pronounced in
3 patients receiving both anti-NGF agent and NSAIDs
4 concurrently, but it's clearly present in both
5 treatment groups. The occurrence of these events
6 was markedly disproportional, favoring drug
7 treatment over placebo treatment, which supports
8 that these events of joint destruction are related
9 to drug treatment and not occurring as part of the
10 natural history of OA. In fact, some cases
11 occurred in patients without a history of OA, which
12 further supports this conclusion."

13 Sixth, the sponsors of the three agents seek
14 to market them for treating chronic pain due to
15 numerous common conditions. Widespread use of
16 these drugs in the expected target population will
17 result in an epidemic of anti-NGF-induced
18 arthropathy.

19 In conclusion, data for the anti-NGF agents
20 confirms the appropriateness of FDA's decision to
21 place studies of these agents on clinical hold.
22 There is no further role for the further

1 development of these agents for anyone with OA.
2 There are FDA-approved agents with demonstrated
3 efficacy and acceptable risk-benefit profiles for
4 treating OA. In contrast, anti-NGF agents have
5 been shown to have an unacceptable risk-benefit
6 profile.

7 These agents intended to treat a symptom of
8 a non-life-threatening disorder can actually
9 accelerate the underlying disease process.
10 Avoidance of co-treatment with NSAIDs and use of
11 lower doses will not sufficiently limit this risk.

12 Two, there is also no role for ongoing
13 development of these agents for chronic pain from
14 other conditions. Many patients with other
15 disorders causing chronic pain have OA, a common
16 disorder, and thus would be at risk for developing
17 these complications. Furthermore, the adverse
18 effects on joints can occur in the absence of OA.

19 Given the existing data showing a serious
20 and unusual safety signal with anti-NGF agents, it
21 is inconceivable that FDA would approve these drugs
22 for long-term treatment of chronic pain and further

1 research should not occur. Thank you.

2 DR. BUCKLEY: Thank you, Dr. Carome.

3 We think speaker number 2 is not here, so
4 we'll proceed to speaker number 3.

5 [No response.]

6 DR. BUCKLEY: We'll go on to speaker
7 number 4, if you're here.

8 [No response.]

9 DR. BUCKLEY: Speaker number 5?

10 [No response.]

11 DR. BUCKLEY: A number of speakers haven't
12 actually registered, so we're checking to see who's
13 here.

14 Speaker number 6?

15 [No response.]

16 DR. BUCKLEY: Speaker number 7?

17 [No response.]

18 DR. BUCKLEY: Maybe 8 is the magic number.

19 Speaker number 8?

20 MR. PHILLIPS: Hello. My name is Julian
21 Phillips, representing U.S. Pain Foundation as an
22 ambassador of the foundation. Nicole Hemmingway is

1 one of the directors who wrote the book, "No, It's
2 Not In My Head." We're not really here
3 representing the OA and what you're putting forward
4 here, but rather that pain medications and research
5 needs to continue on an ongoing basis with more
6 than we see presently.

7 I'm a patient of chronic pain. I have
8 RSD/CRPS. And what I see out there is more of the
9 same. Just take another one of these NSAIDs. Take
10 another opiate. There's nothing new coming on the
11 market. There's no new research -- or apparently
12 there's no new research -- for painkillers and for
13 help when you consider that there are \$560 to \$650
14 billion a year in healthcare and productivity
15 losses because of pain related to nursing home,
16 military personnel, lost tax revenues, et cetera.

17 Significant savings could be released
18 through improvements in pain prevention, care,
19 education, and research. Acute pain, if left
20 untreated, often becomes lifelong pain. Early and
21 appropriate intervention can help prevent this
22 result and significant savings.

1 Chronic pain is a disease unto itself. And
2 when we say chronic pain is a disease, there's
3 people in here who have probably got pain. If I
4 didn't have this sleeve cut off, nobody has the
5 slightest idea that I've got pain. Nobody
6 understands that I'm in pain 24 hours a day, seven
7 days a week, ranging from -- and I can't remember
8 what the scale is called -- ranging from 5 through
9 to 10.

10 Nobody understands that it's not just in
11 here; it's in the neck. RSD spreads and cannot be
12 seen. And as a result, we don't get the amount of
13 research into medications that we should be
14 getting. And the U.S. Pain Foundation's goal is to
15 become visible for pain patients.

16 I appreciate it has nothing completely to do
17 with what you're discussing today, but it's
18 something that we need to draw to the FDA's
19 attention.

20 DR. BUCKLEY: Thank you, Mr. Phillips.

21 Speaker number 9?

22 MR. GINSBERG: Hello. My name is Seth

1 Ginsberg. I'm the president of the Global Healthy
2 Living Foundation. I have no disclosures to make
3 today regarding my travel here. The GHLF accepts
4 grants and charitable contributions from many
5 sources, including pharmaceutical companies,
6 government agencies, private foundations, and
7 individuals.

8 Good afternoon. On behalf of the Global
9 Healthy Living Foundation, I want to thank the
10 Arthritis Advisory Committee for allowing me to
11 speak today. GHLF is a 501(c)(3) patient advocacy
12 group that represents more than 50,000 members with
13 our arthritis webpage, creakyjoints.org, and more
14 than 20,000 Facebook fans on our creaky joints
15 page.

16 I was diagnosed with spondyloarthropathy at
17 13. At 15, I was a national spokesperson for
18 arthritis. And 12 years ago, at 18, I co-founded
19 the GHLF. That makes me 30 today. And after
20 27 years in pain, I know that if the Greeks hadn't
21 created Sisyphus, pain patients would have. But
22 our king would not be a myth.

1 I'm here today to speak in favor of resuming
2 the phase 3 trial of tanezumab, which was suspended
3 in 2010 after evidence of necrosis in
4 osteoarthritis patients. We've heard about NSAID
5 interactions as well as increased patient activity
6 that may have caused the necrosis. To us, these
7 are fairly simple to fix.

8 You see, when Porsche invented its model 959
9 in 1986, it was the fastest street-legal car in the
10 world. The Porsches were rear-ending other cars at
11 high speeds when drivers underestimated the power
12 of the all-wheel-drive turbo-charged car. The
13 solution was simple, more sensitivity to achieving
14 desired results with less gas pedal.

15 The Wall Street Journal and others reported
16 on the theory that the clinical trial necrosis was
17 caused by patients overusing and then wearing out
18 their arthritic knees because they didn't feel the
19 pain that ordinarily would have limited movement.

20 If this is the case, the solution is simple,
21 more sensitivity to the benefits and
22 responsibilities of being pain-free. If this is

1 the case, we have an opportunity to create new
2 rules among pain patients who want to redefine
3 quality of life and successful treatment.

4 The medical community has been here before.
5 Contact lenses provided near-perfect vision.
6 However, they must be removed, cleaned, and thrown
7 away or the wearer can suffer permanent eye damage.
8 Contact lens wearers know this.

9 I believe I speak for our thousands of
10 members in pain when I say, give us the chance to
11 learn how to be pain-free. If it means tempering
12 our activity, that is better than being the absurd
13 hero, as Albert Camus called Sisyphus, struggling
14 perpetually and without hope of success.

15 Thank you very much for allowing me to speak
16 today on behalf of our Creaky Joints and Global
17 Healthy Living Foundation members. We urge the
18 committee to approve the continuation of phase 3
19 trials of tanezumab, as well as NGF inhibitor-class
20 drugs. Have a good day.

21 DR. BUCKLEY: Thank you, Mr. Ginsberg.

22 Speaker number 10?

1 [No response.]

2 DR. BUCKLEY: And are there any speakers who
3 arrived late, who are registered and would like to
4 speak?

5 [No response.]

6 DR. BUCKLEY: The open public hearing
7 portion of this meeting has now concluded, and we
8 will no longer take comments from the audience.
9 After a break, this committee will turn its
10 attention to address the task at hand, the careful
11 consideration of the data before the committee as
12 well as the public comments.

13 We'll take a 10-minute break and be back at
14 10 after.

15 (Whereupon, a brief recess was taken.)

16 **Clarifying Questions to Sponsor and FDA (con't)**

17 DR. BUCKLEY: So for about 20 minutes, we're
18 going to try and finish up on the clarifying
19 questions. We're going to start with the
20 clarifying questions to the sponsor, and then we'll
21 finish up on the clarifying questions to the FDA.
22 We have a list of people who have been waiting to

1 speak. We may be able to add a couple of names to
2 that list, but we're going to try to keep this,
3 since it's mostly clarification, as brief as we
4 can.

5 So again, to start with questions to the
6 sponsor, Dr. Blumenthal?

7 DR. BLUMENTHAL: David Blumenthal.

8 Dr. Verburg, if you are here, Dr. Schnitzer showed
9 us some data on the effect size with some of the
10 comparator drugs for pain. Can you share with us
11 the effect size in these studies for tanezumab,
12 especially in the doses that might be used in
13 future trials? If you're not going to use the
14 10-milligram dose because of possible toxicity,
15 we'd be interested in some of the lower doses for
16 the outcome measures that were used.

17 DR. VERBURG: This is the effect size of
18 tanezumab 2.5, 5, and 10 milligrams, and naproxen
19 versus placebo. And this is, as you can see, the
20 effect sizes by study, so the four studies and then
21 pooled down at the bottom. And then I think it's
22 fairly clear that all of them provide effect sizes

1 of .5 or greater with a little bit of a diminution
2 in the 2.5-milligram dose relative to the others,
3 but not substantial.

4 DR. BLUMENTHAL: Then a question about
5 safety, it's not clear to me at what point in the
6 study it became apparent that some patients were
7 getting something that was not the customary
8 progression of osteoarthritis.

9 Do you have something like the median time
10 of clinical discovery, or median time until
11 discontinuation of drug, or something like that,
12 that gives us an indication at what point the
13 patients developed this problem?

14 DR. VERBURG: In the terms of the process
15 itself, it certainly wasn't systematic. I mean,
16 basically, you can trace back the early signals of
17 the event in terms of investigators reporting
18 adverse events, which were serious adverse events
19 described as osteonecrosis, leading to total joint
20 replacement, about early 2010, and they picked up
21 from there.

22 That just so happened to be, in terms of

1 enrollment, about three-quarters or so of our
2 program enrolled. So in sort of a chronology
3 fashion, that's how the signal detection worked.
4 It wasn't anything systematic other than, those
5 reports began to accumulate. And initially,
6 because most of the patients were on either
7 tanezumab monotherapy or tanezumab NSAID
8 combination therapy,. when those treatments were
9 unblinded, because they were unexpected events,
10 they were all associated with tanezumab treatment.

11 DR. BLUMENTHAL: Actually, I was referring
12 to -- sorry I didn't clarify -- the patient's
13 perspective, how long they had been exposed to
14 either active drug or a comparator at the time that
15 they were either taken off active drug or qualified
16 to be called one of these non-OA events.

17 DR. VERBURG: Yes. So the slide that
18 I'm -- probably I ought to just go to rapidly
19 progressive osteoarthritis to answer that, B-167.

20 Yes. If we can show this slide, please.

21 So this is a distribution of the events of
22 rapidly progressive osteoarthritis, so these are

1 events adjudicated by the committee as a function
2 of the number of doses that the patient received in
3 the phase 3 OA trials.

4 So you see there in the blue bar are
5 patients treated with tanezumab monotherapy, and
6 those treated with the green bar receiving
7 tanezumab in combination with NSAID therapy, and
8 then the one case of rapidly progressive
9 osteoarthritis with NSAID treatment alone.

10 So there is a gradual increase that's maybe
11 apparent, more so with combination therapy than
12 not, but these events seem to be sprinkled
13 throughout the dosing, the number of doses that the
14 patients have taken.

15 DR. BLUMENTHAL: Thank you.

16 DR. BUCKLEY: Dr. Clemens?

17 DR. CLEMENS: That answered my question.

18 DR. BUCKLEY: Dr. Kelly?

19 DR. KELLY: Yes. A basic science question
20 for Dr. Braunstein regarding the animal data.
21 There was a mention of cartilage area and optical
22 density in this meniscectomy model with RGN475.

1 And I just wanted to clarify, that doesn't mean
2 much to me.

3 Does that suggest proteoglycan content,
4 cartilage integrity, matrix integrity, or just an
5 area measurement?

6 DR. BRAUNSTEIN: So I am going to introduce
7 Dr. Susan Croll, who's our biologist, who did these
8 experiments, so she can help the committee with
9 that.

10 DR. CROLL: So just to make it clear, all
11 that we did is look at histological slides with
12 safranin O staining. So the safranin O, for those
13 if you who are unfamiliar with this stain, is the
14 red stain. And there's a fast green counter-stain
15 so that you can see the rest of the tissue,
16 particularly the bone.

17 The red stain that goes all the way across
18 the top is the growth plate, and the bone marrow
19 also stains a little bit red. But the areas that
20 are right adjacent to the joint space are the areas
21 of cartilage. And I have shown here a tracing of
22 the cartilage area. And this is simply how we do

1 it, is using ImageJ quantitative software, we go
2 through and we actually measure the area that's
3 occupied by cartilage as stained by safranin O, and
4 that in those areas that have the cartilage, we do
5 an optical density measurement.

6 So this does not say anything about
7 cartilage function. It does not say anything about
8 cartilage volume unless you calculate serial areas.
9 All that it says is, within these structures, this
10 is the area of cartilage that we're seeing and the
11 density within that area of safranin O positive
12 staining.

13 DR. KELLY: Thank you.

14 DR. BUCKLEY: Dr. Gerstenfeld, do you have
15 another question?

16 DR. GERSTENFELD: No.

17 DR. BUCKLEY: No? Okay.

18 I think Dr. Suarez-Almazor had a question
19 about the x-rays.

20 DR. SUAREZ-ALMAZOR: Yes. If at all
21 possible, I'd like to see the data on x-rays that
22 you had for that trial, the way it was done. And I

1 also had a question in relation to efficacy, if I
2 can go ahead and ask it while you look for the
3 data.

4 If I calculate correctly the number needed
5 to treat, the efficacy of the drug versus NSAIDs,
6 the number needed to treat, it's about 10. So we
7 need to treat 10 patients to have 1 patient improve
8 at 50 percent.

9 Is that correct?

10 DR. VERBURG: It's a little bit lower than
11 that, but you're very close. It's actually on the
12 order of 6 to 7, depending on the dose. And that's
13 for a 50 percent response.

14 DR. SUAREZ-ALMAZOR: At 50 percent, yes; 1
15 out of 10 will improve beyond --

16 DR. VERBURG: Yes, approximately so.

17 So back to your first question, which was
18 you'd like to see the sequential radiographs, we'll
19 begin here. This is B-396. I'm going to take you
20 through the patients that had -- the index hip was
21 identified as the hip. And first of all, I'm
22 showing the distribution of the hip cohort in

1 study 1025, so there were 458 patients total. And
2 what I'm showing you is the joint space width
3 change between baseline and end-of-study x-ray.
4 The average or median time was 337 days. So,
5 again, I want to make sure that everybody is clear
6 that the objective of getting all patients with a
7 one-year radiograph was not met because of the
8 hold.

9 So you see here the KL scores up at the top,
10 and the mean baseline joint space width, and the
11 mean joint space width change, and the median
12 exposure is there. And this is just sort of a
13 quintile distribution of the joint space changes
14 that occurred.

15 Next slide, please. Please show this slide,
16 397.

17 So if you go back to the OARSI-OMERACT
18 definition of how to interpret radiologic
19 progression in knee or hip osteoarthritis, they set
20 some criteria in which one needs to identify what
21 the experimental measurement threshold of your
22 procedure is in order to be able to identify what

1 in fact you can identify as progressors in your
2 study.

3 That was indeed done with this cohort of
4 patients, and you can see that, by definition that
5 was used, the standard, that the change had to be
6 1.08 millimeters or greater. And you see the
7 dotted line there identifies that. So 18 out of
8 these 331 patients were identified as having
9 clinically demonstrable progression.

10 Next slide. So if we now take those results
11 and put those into the treatment assignments, which
12 I'm sure everybody is interested in, this is the
13 analysis of those broken down by tanezumab alone,
14 two doses of tanezumab plus NSAID. Again, these
15 were randomized patients to that treatment group
16 and NSAID alone.

17 You can see that because the variability was
18 quite high, the cutoff for determining progression
19 was actually quite high. The numbers shrink
20 dramatically. But there's nothing in that dataset
21 that suggests that there's anything substantially
22 different about the progression of patients

1 receiving tanezumab treatment versus those that
2 received NSAID treatment alone.

3 Now, just one more slide, and then I'll move
4 on. B-402. Yes, please go ahead and show this.

5 So this is from the ECHODIAH trial, done
6 several years ago now by Maxime Dougados and
7 colleagues. In fact, Dr. Vignon, who's here today,
8 I think participated in this trial as well. This
9 was sort of an apples-to-apples comparison now, so
10 this is a trial with diacerein in the hip, followed
11 for a couple of years.

12 Again, I'm just showing you just to show you
13 what the progression of patients were in the trial,
14 and then putting in some arbitrary cut points to
15 show you what the patients that progressed at
16 1 millimeter or more, or 2 millimeters or more in
17 this hip study look like, just to put the tanezumab
18 effects into perspective.

19 DR. SUAREZ-ALMAZOR: Do you have mean
20 difference by group, not just how many progressed,
21 more than one?

22 DR. VERBURG: Can I see B-417, please?

1 So this is the change in hip joint space
2 width by mean change. So baseline means you see
3 there in the second row. Mean joint space width
4 change, you can see for all the groups, and then
5 whether or not there was any statistical difference
6 between the groups. And you see that there was one
7 difference between tanezumab 5 milligrams given in
8 combination with NSAIDs.

9 DR. SUAREZ-ALMAZOR: Sorry. Can you leave
10 it on just for a second?

11 DR. VERBURG: Yes. Sure.

12 Could you put the slide back up?

13 DR. SUAREZ-ALMAZOR: So the p-value is
14 comparing what with what?

15 DR. VERBURG: The p-value is comparing each
16 tanezumab treatment group to NSAID.

17 DR. SUAREZ-ALMAZOR: So it's the column on
18 the right?

19 DR. VERBURG: The column on the far right.
20 Correct. Thank you.

21 DR. BUCKLEY: Dr. Morrato?

22 DR. MORRATO: Yes. Elaine Morrato. I had a

1 clarifying question as it related to risk
2 minimization and the recommendation that patients
3 who do not adequately respond should discontinue
4 therapy. And I was hoping the sponsors might
5 clarify how they propose defining that and when
6 might that be assessed. As I understand the dosing
7 schedule, I think it's every eight weeks.

8 So I'm wondering, then, how the handling the
9 risk of a patient who might, in that eight-week
10 period, not respond and resume NSAID therapy, how
11 are you planning and sort of operationalizing this
12 out in a clinical practice setting, not in a trial
13 where you might have more frequent office visits
14 for the trial.

15 DR. VERBURG: It is true. I mean, the
16 half-lives and the dosing intervals for the
17 compounds range from 4 to 8 weeks, and in some
18 cases, 12 weeks. So again, we've done this from an
19 evidence-based point of view. We've gone back to
20 look to see whether a patient responds after one
21 dose, in fact will respond after two doses, and if
22 so, what's the positive predictability of that and

1 what's the false negatives that occur.

2 DR. MORRATO: So how are you defining
3 response, then?

4 DR. VERBURG: I was just getting to that.
5 We have defined response level in two different
6 ways. Not surprisingly, we've taken a WOMAC-pain
7 30-percent reduction, which I think people
8 generally think is sort of a minimal response. And
9 we've also utilized the 50 percent response.

10 I think that's a matter of some discussion.
11 And actually some input that we'd like to have is
12 what would a meaningful response be on an
13 individual basis where one could make that judgment
14 clinically, and then evaluate the patient as to
15 whether or not they "met the response level" or
16 not. And it's always an N of 1 experiment, and
17 that's what I think makes it a little difficult to
18 put it into practice.

19 DR. MORRATO: Then the other question I had
20 was just a follow-up on the efficacy. I think that
21 Dr. Blumenthal was asking, and you presented a
22 slide. And I wasn't sure. Was that all trials?

1 Was that just the OA trials? Because I remember a
2 slide in which you show dose response in the
3 chronic low back pain studies, and the 5-milligram
4 was not affected, at least on one -- or two of the
5 three measures.

6 DR. VERBURG: Let me clarify that slide. It
7 probably went up and down too fast. That was the
8 four placebo-controlled trials, evaluating 2.5, 5,
9 and 10 milligrams. So I put that slide up because,
10 as we suggested, we're very interested in
11 progressing 2.5 and 5 milligrams. And we want to
12 make sure that the committee is aware of just how
13 efficacious 2.5 is, since there was no cases of
14 rapidly progressive osteoarthritis, in fact, in
15 that dose.

16 DR. MORRATO: But was that in OA patients?

17 DR. VERBURG: Just in OA patients. Exactly.

18 DR. MORRATO: So are you thinking the same
19 dose range, then, for the chronic low back pain?
20 Or how are you thinking of managing that? I
21 understand it's a tradeoff.

22 DR. VERBURG: I think it's a very good

1 question, and I think it will come up later in the
2 discussion today. I mean, there's no reason to
3 assume a priori that the dose schedule or the dose
4 range that we have, that's appropriate for OA,
5 would be applicable to low back pain. In fact, it
6 doesn't look so. And a submaximal efficacious dose
7 does not declare itself, obviously, in one study.
8 And in fact, typically, it's not that you just get
9 a graded response, but in some trials, you'll see
10 almost no response, and then in the next trial,
11 you'll see a large response.

12 So I'm not ready to park 5 milligrams in
13 chronic low back pain yet. I'd want to study it
14 some more. I certainly don't think I need 20. So
15 right now, my dose range in chronic low back pain
16 would be 5 and 10 milligrams, but that 10-milligram
17 dose is higher than what I am proposing to take
18 into osteoarthritis patients.

19 DR. MORRATO: Thank you for clarifying.

20 DR. BRAUNSTEIN: I just wanted to clarify
21 that not all the sponsors are pursuing Q8-week
22 dosing. So we're looking at shorter intervals in

1 lower doses as one of the strategies. So that
2 also -- in thinking about this -- I know you said
3 everybody was eight weeks, but that's not
4 necessarily going to be the way we're going
5 forward.

6 DR. BUCKLEY: Dr. Neogi?

7 DR. NEOGI: I had a question about the
8 neurologic symptoms. If I understood correctly,
9 none of the rapidly progressive OA or joint
10 replacement cases seemed to have had differential
11 neurologic symptoms.

12 I was wondering if the participants had a
13 structured neurologic exam in addition to the
14 self-reported symptoms, and, in particular, I'm
15 interested in proprioception.

16 DR. VERBURG: I think the sponsors have some
17 very useful information to bring to bear on that.
18 I'm going to bring a couple of my colleagues up, I
19 think, to answer two questions about the overall
20 landscape, but also what was the neurological
21 assessment of the patients that went on to rapidly
22 progressive OA, because that has come up this

1 morning in terms of potential mechanism.

2 DR. BUCKLEY: And I'll just remind you to
3 just give your name as you make comments.

4 DR. BROWN: Certainly. Good afternoon. My
5 name is Mark Brown. I'm a clinician on the
6 tanezumab program at Pfizer. I'm a neurologist by
7 training.

8 Could I preview slide D-105, please?

9 So to initially answer your question,
10 neurologic safety has been a key component of the
11 tanezumab program since the very beginning. And to
12 directly answer your question, yes. Every patient
13 that came in, in our clinical trials in tanezumab,
14 had a structured neurologic examination that
15 included a standard assessment of cranial nerve,
16 motor, deep tendon reflexes, and sensory function.

17 These exams were reported on a standardized
18 instrument known as the neuropathy impairment
19 score, which was developed by Mayo Clinic and has
20 been used widely in clinical trials, looking for
21 evidence of neuropathy or signs of a neuropathy.

22 So as we begin to look at patients with

1 rapidly progressive OA, we heard a lot of
2 discussion this morning about sensory loss in
3 patients with or without the condition.

4 Could we go ahead and show now slide D-105?

5 I think what I'd like to show here is, we
6 specifically looked at sensory examination findings
7 in the lower extremities, both for those patients
8 with RPOA and those without RPOA, across our entire
9 OA program, including both the phase 3 controlled
10 and the long-term OA studies.

11 I'll draw your attention down to the bottom
12 footnote that describes the NIS, the neuropathy
13 impairment score. And when we look at the subset
14 of that score, focusing on sensation in the lower
15 extremities, we see that a totally normal
16 examination with respect to joint position sense,
17 vibration, and pinprick in these patients would be
18 a score of zero; whereas if you had totally absent
19 joint position sense, vibration, and pinprick in
20 both great toes, you would have a total score of 12
21 on this score.

22 It's important to realize that if someone

1 has insensitivity or a substantial neuropathy
2 causing lack of sensation at the knee or the hip,
3 that it's really appropriate to look at the great
4 toes as the first place where you would begin to
5 see these effects.

6 So this is a very sensitive way to look at
7 sensation. And you'll see that when you compare
8 those 66 OA patients, all treated with tanezumab
9 with RPOA at baseline, a score of .24, which is
10 very nearly zero, compared with .32 for the entire
11 rest of the OA population without RPOA, if you look
12 then at the mean change from baseline, from their
13 baseline to their final neurology score, you see
14 very, very small changes, .02 and .08. And I would
15 say that these are actually slight improvements
16 rather than demonstrable decreases.

17 So in both of those conditions, you see the
18 p-value is clearly .5. So I think that's telling
19 us that there are not substantial changes in the
20 RPOA sensation in the feet and the legs of these
21 patients compared with the non-OA population.

22 To take that one step further, we also

1 looked at patients in our program. Anytime there
2 is a patient reporting an abnormal sensation or a
3 significant change on neurologic exam, those
4 patients were to be referred for a neuro
5 consultation with neurologists dedicated to
6 evaluating these patients.

7 If I could preview then D-113. Please show
8 D-113.

9 We then looked at those patients that had
10 both a joint safety adjudication and some reason to
11 have a neurologic consult. And Dr. Martin
12 Koltzenburg from Queens Square behind me was the
13 person that reviewed these. Dr. Koltzenburg
14 reviewed these patients without knowledge of the
15 study treatment or the adjudication outcome and
16 then provided a diagnosis in each of these cases
17 wherever possible.

18 So if we could display D-114. These are the
19 results that we came down to. So as you'd heard
20 earlier, we had 249 patients with joint safety
21 adjudication results. Out of those, 78 percent of
22 the patients did not have a neurologic consultation

1 because they did not report any sort of abnormal
2 sensation events or did not have any substantial
3 change on their neurologic exam by the
4 investigators. So that leaves 54 patients who had
5 both an adjudication outcome and a neurologic
6 consultation, or 22 percent of the total.

7 What we've shown here on the left-hand
8 column is the adjudication outcomes for all 54 of
9 those patients. And across the columns, we've
10 demonstrated the neurological diagnoses that fell
11 out from those.

12 So I would point out just three things here.
13 First, the normal column. You see that of the 54
14 patients, approximately half of them were
15 neurologically normal at the time of their
16 consultation.

17 Another finding is at the bottom of the
18 carpal tunnel row. When we're finding patients are
19 going for neurologic evaluations, oftentimes,
20 they're being diagnosed with carpal tunnel or other
21 mononeuropathies that clearly are not part of any
22 sort of hip or knee pathology.

1 Then finally, at the very far end on the
2 right, there was a total of one patient diagnosed
3 with osteonecrosis or rapidly progressive OA that
4 had a polyneuropathy. So overall, the results are
5 not consistent with these RPOA patients having a
6 substantial sensory deficit or neurologic deficit
7 that's driving their neurologic findings.

8 Dr. Koltzenburg --

9 DR. BUCKLEY: I'd like to just interrupt.
10 We have a number of people, different sponsors, up
11 at the microphone, and I just want to organized and
12 get through this.

13 Do the two speakers currently standing want
14 to address Dr. Neogi's answer to her question?

15 Yes. And are you from Janssen? Could you
16 introduce yourself?

17 DR. THIPPHAWONG: Hi. I'm John Thipphawong
18 from Janssen R&D. We also did extensive neurologic
19 testing prior to every dose and at regular visits
20 in all subjects. This included looking at the MMSC
21 and also a complete neurologic examination prior to
22 every dose.

1 Slide up, please. On this slide, we have a
2 summary of the peripheral neurologic adverse events
3 broken down by whether they developed our
4 adjudication of RPOA, joint replacement without
5 RPOA, and non-JR. And as you can see here, there
6 does not appear to be a relationship between the
7 development of peripheral neurologic adverse events
8 and the development of RPOA.

9 Next slide. In addition to the neurologic
10 examination, we conducted, similar to Pfizer, a
11 very structured examination of all peripheral
12 joints, including legs and hands. This was done
13 with a total neuropathy score nurse, which includes
14 questions and examinations looking at sensory
15 abnormalities, motor abnormalities, autonomic
16 abnormalities in a structured examination of every
17 limb, with pin sensibility and vibration sense.

18 A change of 2 or 3 on each subscore or 3
19 overall was considered clinically significant.
20 I'll just state for brevity that we did not see a
21 relationship in patients with RPOA versus those
22 that did not have a joint replacement.

1 DR. BUCKLEY: Thank you. The third
2 microphone?

3 DR. BRAUNSTEIN: Yes. I want to George
4 Yancopoulos, our chief scientific officer. He was
5 involved in some of the original neurotrophin
6 cloning research, and he has some important
7 comments he wants to make from the scientific
8 perspective about this question.

9 DR. YANCOPOULOS: Yes. I think the
10 question, which started out about proprioceptive
11 function, is an incredibly important one,
12 especially in light of some of both data and
13 potential causes that were brought up by Joan
14 Bathon, where she showed these dramatic
15 subluxations and posited that, in fact, tendon
16 dysfunction and subluxation could somehow be
17 involved in the mechanism.

18 I think everybody should really understand
19 that there is a family of very related growth
20 factors here. An NGF that everybody is focusing on
21 is working on a certain type of sensation, but not
22 on proprioception.

1 It turns out that another factor,
2 neurotrophin 3, is very specific and very important
3 for proprioceptive function. And one sees,
4 actually, some very dramatic dislocations and
5 proprioceptor dysfunction in animals that are
6 lacking NT-3.

7 So I think it is very important to consider
8 the possibility that some of these agents might
9 have some effects on neurotrophin 3, and that
10 might, according to Joan Bathon's speculations,
11 contribute to some of the mechanisms here.

12 So this may not be purely an anti-NGF-type
13 of side effect that is leading to this rapid
14 progressive destruction of joint, but rather,
15 perhaps, actions that are specific to the joint,
16 maybe to the diseased joint, just because standard
17 measures, vibratory, and so forth of the great toe
18 and so forth are normal. It doesn't mean that the
19 disease joint is normal in terms of proprioceptor
20 sense and how it might contribute to the demise of
21 the joint.

22 I don't know if we'd want Joan Bathon

1 to -- I'd like to hear her comment further in the
2 background of understanding that NT-3 is very
3 specific for proprioceptor function; could that
4 actually be contributing to the picture that one
5 sees here in terms of the rapid joint dysfunction,
6 if one --

7 DR. BUCKLEY: I think, in terms of our
8 limited time, I appreciate your observation.

9 Dr. Neogi, your question's answered?

10 DR. NEOGI: Yes.

11 DR. BUCKLEY: So I think we'll move to the
12 next speaker. Dr. Leff -- or next question?

13 DR. LEFF: Yes. Hi. Rich Leff. I had a
14 question to try to get us on the page in terms of
15 case definitions and the like. And a lot of people
16 looked at bad outcomes from patients in the
17 studies. And would I be correct in saying that in
18 the sensitivity analysis, for Dr. Verburg, where
19 you included patients that were hard to
20 characterize or categorize, that that included ones
21 that Dr. Bathon or others considered as bad
22 outcomes?

1 DR. VERBURG: Yes. I have provided several
2 analyses, sensitivity analyses, this morning. But
3 the one that you saw at the very end of my
4 presentation around the risk minimization
5 procedures, the left panel of that slide was, in
6 fact -- I had called it a composite endpoint. And
7 as best I can tell from Dr. Bathon's and from
8 others' work, that is sort of all of the
9 adjudication endpoints that fall into a bad
10 category, however one has defined it.

11 DR. LEFF: Dr. Bathon, would you sort of
12 agree to that or do you think that's -- I'm just
13 trying to see if we're on the same page with regard
14 to the data.

15 DR. BATHON: I guess the one caveat would be
16 whether those insufficiency fractures were included
17 in the sensitivity analysis, because sometimes
18 those were rated by the committee as other.

19 DR. VERBURG: They were. Maybe let's go
20 back up to this slide real quick, and we'll see if
21 we can ground this out, A-54.

22 So this slide on the left -- and this is now

1 frequency, not event rate, so this is provided as
2 percent of patients. And again, this is termed a
3 "composite endpoint." This includes all-cause
4 total joint replacements that were adjudicated to
5 osteonecrosis, rapidly progressive OA, and the 10
6 patients where the committee adjudicated the
7 outcome to subchondral insufficiency fracture.

8 DR. BATHON: Yes. The other category that I
9 think might have fallen through the cracks was the
10 SPONKs.

11 DR. VERBURG: The SPONKs, in our particular
12 adjudication, would have been subchondral
13 insufficiency fractures.

14 DR. BATHON: They were.

15 DR. VERBURG: There were 10 of them. They
16 all occurred in the knee. And although the
17 committee made reference to the terminology,
18 "SPONK," realizing that that was somewhat of a
19 misnomer based on the other work that's gone on
20 subsequently, those got kind of renamed, if you
21 will, to subchondral insufficiency fracture.

22 So I can't come up with the exact fit of all

1 of the numbers, but I think that somewhere between
2 80 and 90 events are the events that people have
3 identified as being unusual, and I think this is
4 pretty close to representing that group of events.

5 DR. BUCKLEY: Second microphone

6 DR. BATHON: I think that's true.

7 DR. BUCKLEY: Yes. Go ahead.

8 DR. COLBURN: You said this is the adverse
9 events as reported per patient, not per joint; is
10 that correct? And not only is it per patient, but
11 it is per patient who went on to a total joint. So
12 that actually leaves out certain joints. It leaves
13 out cases that did not go on to total joint
14 replacement.

15 Is that correct?

16 DR. VERBURG: No, no. That's not correct.
17 It is per patient. Okay? It is on a per-patient
18 basis.

19 DR. BUCKLEY: Thank you.

20 DR. VERBURG: But it does include patients
21 that did not or did go on to total joint
22 replacement, and it was irrespective of that.

1 DR. BUCKLEY: Thank you very much.

2 Second microphone?

3 DR. UPMALIS: Thank you very much, Doctor.

4 I would like to just remind the committee
5 that we're looking at data that were collected
6 retrospectively. And with all due respect, we have
7 two reviews on behalf of the FDA, one looking at
8 paper copy -- slide up, please -- and one which was
9 the review of a single practitioner.

10 Our adjudication, which is similar to the
11 Pfizer adjudication, utilized a panel of experts in
12 their field, as you can see here. And if I may,
13 I'd like to ask Dr. Michael Mont just to come up
14 and speak about the panel's experience.

15 DR. MONT: Thank you. I'm Michael Mont.
16 I've received honoraria from Janssen, but I have no
17 financial interest in their company or the results
18 of this whole adjudication board.

19 We went through cases over about a year
20 period with all these members, about seven members.
21 We met on a number of occasions. We actually saw
22 the original films, and that may be is what is some

1 of the differences and what was occurred with the
2 FDA adjudication.

3 In all the 18 cases of RPOA that we
4 adjudicated, we had complete consensus. I think
5 the confusion occurs when you start looking at
6 radiology reports and the radiologist reads this
7 as, "Can't rule out osteonecrosis," or believes
8 this is osteonecrosis.

9 There were also a number of pathology
10 reports that say this is osteonecrosis. But when
11 we actually examine it, you are seeing areas of
12 osteonecrosis or areas of dead bone. And we know
13 that in any type of osteoarthritis or in RPOA,
14 between 10 and 30 percent of those specimens, when
15 you retrieve the femoral heads during surgery,
16 you're going to see areas of dead bone, and it can
17 be labeled as osteonecrosis. And I think that's
18 where some of the confusion is occurring.

19 We also had -- in the 18 cases, four to five
20 of the cases had MRIs or CT scans, and those are
21 typically 99 percent sensitive and specific for the
22 diagnosis of osteonecrosis. And they were read as

1 negative for osteonecrosis, even when, later, there
2 were pathology reports showing dead bone.

3 So I think that's where some of the
4 confusion is. I don't want to downplay the fact
5 that there is this increased signal for something,
6 for RPOA, but I can also tell you that when I do
7 hip and knee surgery, I see RPOA. I follow these
8 patients about 5 to 10 percent of the time. And
9 that really severe type, that type 2 which is not
10 really named yet, that muralytic type, I still see
11 that as a tertiary center in Baltimore or at
12 Hopkins about 3 percent of the time. So it is not
13 uncommon to see this and it has been reported.

14 So thank you for your attention.

15 DR. BUCKLEY: Next question from Dr. Boyce.

16 DR. BOYCE: We have had some speculation
17 today about the possible mechanism whereby these
18 agents, in combination with NSAIDs, could be
19 leading to this rapid necrosis. So my question was
20 whether any of the sponsors had pre-clinical data
21 to examine interactions between these two to try
22 and give us some pathogenetic mechanism here.

1 DR. UPMALIS: David Upmalis at Janssen. We
2 have not had the opportunity -- first of all, our
3 molecule is human, and therefore the only animal
4 model would be a non-human primate. Unfortunately,
5 in that species, there's really no validated
6 osteoarthritis model that we can test this in.

7 DR. BUCKLEY: Next microphone?

8 DR. BRAUNSTEIN: So we actually did an
9 experiment in mouse that I alluded to. This is in
10 your addendum to the briefing book, involving a
11 pilot study where we used the destabilized medial
12 meniscus model and evaluated the effects of RGN475
13 alone or in combination with indomethacin.

14 I alluded to two basic findings in this
15 study. Slide on.

16 One finding was that the combination of
17 RGN475 plus indomethacin, but not RGN475 alone or
18 indomethacin alone, resulted in elevation in
19 tartrate-resistant acid phosphatase 5b or TRAcP 5b,
20 which is a serum marker of osteoclast activity.

21 These are the data. As you can see, this
22 elevation is seen with this drug combination,

1 regardless of whether or not the animals have the
2 DMM procedure or the SHAM procedure. The other
3 findings, we had seen, I mentioned there was some
4 decrease only in the DMM group with a combination
5 in terms of cartilage area and density. Those were
6 very variable findings, which we really need to
7 look into some more. But I thought I would show
8 this in response to your question.

9 DR. BOYCE: So can I ask, did you look at
10 histologic sanctions for increased osteoclast
11 numbers in the joints or anywhere else in the bones
12 of these mice to explain the increase in TRAcP
13 activity in the serum?

14 DR. BRAUNSTEIN: For that, I'm going to ask
15 Susan to come up.

16 DR. CROLL: We haven't yet had an
17 opportunity to do any staining to actually look
18 specifically at osteoclast in those bones. What
19 we've done is a first step. This is a pilot study
20 that we literally just finished.

21 As a first step, we did send the slides to a
22 pathologist who does not even know what drug was

1 involved in the study, just received each sample as
2 a number, knows nothing about it. And the first
3 evaluation that we got back was just a general
4 evaluation of the periarticular tissues, and
5 inflammation, and infiltrate, and so on. And that
6 showed no difference between the groups, the
7 treatment groups, and the DMM study.

8 She's now been asked to go back and look
9 more specifically at subchondral bone. And once we
10 get those sections back, we hope to be able to
11 actually stain them for TRAcP 5b to see whether or
12 not we can take a look in situ in the bone at the
13 actual osteoclast levels, but we have not done
14 those analyses as of yet.

15 DR. BUCKLEY: This is Lenore Buckley, and I
16 wanted to ask the sponsor a clarifying question in
17 sort of looking forward. I think both sides, the
18 sponsor, and the FDA, and clinicians here have
19 talked about the frustrations and the limitations
20 of the pain medicines we have. People who treat OA
21 know that NSAIDs often lose efficacy after a short
22 period of time. And opioids, patients develop

1 tolerance to, and they have side effects.

2 I think when all of those drugs went through
3 approval, initially the benefits were seeming
4 greater than the risks, but related to tolerance
5 and other effects, we seem to lose some of the
6 benefits of those drugs but maintain or increase
7 risk.

8 One of the things that you have to wonder
9 about with this new class of medicine is, do we
10 have any information about tolerance. Does that
11 develop over time? And perhaps, as importantly,
12 what happens when you withdraw them?

13 You have patients you've taken off study,
14 off drug, and one would wonder if you wouldn't get
15 some kind of exacerbation, maybe even greater than
16 their baseline pain. Have you observed that?

17 DR. VERBURG: Can I preview slide C-152,
18 please?

19 So I'll address the first part of the
20 question first, which is what evidence do we have
21 that the efficacy effect is sustained over a
22 greater period of time than what I saw this morning

1 or presented this morning, which is 16 weeks.

2 This is one example of that. I've got
3 several more if individuals are interested. But
4 you'll recall, in the description of our program,
5 that when patients completed 16 weeks of treatment
6 in a randomized, double-blind controlled trial,
7 they were eligible to participate or go on to
8 participate in a longer-term extension trial.

9 So what we've done here is shown you the
10 randomized treatment, so the gray line is the
11 placebo group, the green line is the naproxen
12 group, and the blue line is the naproxen, the
13 tanezumab 5-milligram group. And then they get
14 switched to treatment all at 5 milligrams,
15 beginning at that second baseline visit. And you
16 can see that the blue line there that represents
17 the tanezumab group stays pretty constant for at
18 least for the period of observation that we have.
19 Again we were intending to carry this experiment
20 out two years to demonstrate that durability of
21 effect but failed to do so.

22 Now, I don't have a slide to answer the

1 second part of your question, but the pattern that
2 we have observed so far is that the return to
3 baseline pain, if you will, following cessation of
4 tanezumab treatment is very gradual. And it kind
5 of -- as you might expect, based on the long half-
6 life, the patient begins to return to pain 8 to
7 16 weeks after they are finished receiving
8 treatment.

9 We don't really see any overshoot of their
10 baseline, but then again, we don't have a large
11 dataset to make that prediction well. But there's
12 no one that has stood out in my mind as rebounding
13 well above the baseline level that they entered the
14 study with.

15 DR. BUCKLEY: Second microphone?

16 DR. UPMALIS: Dr. Buckley, as I mentioned,
17 the 2004 study, the add-on OA study, actually was
18 designed as a two-year placebo-controlled blinded
19 study. And here, we have WOMAC function -- WOMAC
20 pain, WOMAC function, and patient global for the
21 first 48 weeks -- 49 weeks. And we can see that
22 this is also add-on during the extension, but the

1 randomized dose of fulranumab or placebo was
2 maintained during this time. So we can see that
3 the pain scores are maintained uniformly low over
4 these 49 weeks.

5 Next slide, please, 325, we do see, upon
6 discontinuation of drug, that there is some return
7 of pain, but in general, this is not above baseline
8 originally for these subjects.

9 DR. BUCKLEY: Thank you.

10 So we're going to take one more question for
11 the sponsor. Dr. Haque?

12 DR. HAQUE: Mustafa Haque. I just had one
13 question about initial inclusion criteria. It
14 seems like these patients were, for the
15 osteoarthritis wings of the studies, patients with
16 generalized osteoarthritis with a single index
17 joint that was particularly painful.

18 Are there any thoughts, as far as proceeding
19 from here, whether you would localize it to a
20 person who had more a more localized single index
21 joint? And are you going to be monitoring like
22 three or four joints? As some of you had

1 mentioned, one of the issues was now getting x-rays
2 of both shoulders and both knees.

3 DR. VERBURG: Yes. I'll start, and then
4 I'll let Dr. Braunstein take over. I think there
5 is unanimity amongst all of the sponsors that we
6 approached these development programs with the NGF
7 inhibitors much like we did with all other standard
8 NSAID, COX-2, analgesics, identified the single
9 joint, the most symptomatic to the patient, and
10 then I won't say ignore, but we're not following
11 the course of the entire patient's osteoarthritis
12 history.

13 So I think in going future -- and that's
14 part of sort of a pillar of one of our sponsors'
15 path forward, going forward, is to actually do more
16 to assess the patient at baseline and do more
17 during the course of the trial to assess the
18 patient's overall osteoarthritis status.

19 Ned, you can add.

20 DR. BRAUNSTEIN: Yes. No, I think that's
21 actually a very important point.

22 Slide on. In terms of ongoing -- you know,

1 we're going to expand our baseline surveillance.
2 One of the artifacts, if you will, of the study
3 designs is you identify the patient's left knee,
4 for example, because you're going to do a knee
5 osteoarthritis study even though the patient has
6 arthritis in both hips. But you define the knee as
7 the joint of interest, and that's perhaps the joint
8 that you've x-rayed, ignoring the fact that the
9 patient has bilateral hip arthritis.

10 So going forward, at baseline in
11 osteoarthritis studies, we're going to get hip,
12 knee, and shoulder x-rays to start with. And then
13 following patients for all of our studies and the
14 OA studies, there's going to be standardized pain
15 questionnaires. There's going to be annual x-rays.
16 There'll be post-study follow-up so that, even six
17 months after the end of planned study, we plan to
18 do a follow-up. This will be an ITT approach. So
19 we want to have all the patients, whether or not
20 they continue on drug or not, we'll have these
21 kinds of follow-ups.

22 Then importantly, patients who do have joint

1 replacement surgery, those individuals will also be
2 followed up with respect to outcome, so we can
3 actually understand the functional outcome as a
4 result of joint replacement to make sure that the
5 joint replacement is seated well because of the
6 questions related to the actual quality of the
7 bone.

8 DR. BUCKLEY: Thank you.

9 So we'll take a few focused, quick questions
10 to the FDA. On our list, we still have
11 Dr. Khurana.

12 DR. KHURANA: Jasvir Khurana. I just wanted
13 to clarify terminology that we're using. The use
14 of rapidly progressive osteoarthritis,
15 osteonecrosis, are we using them interchangeably?
16 Because the issue of whether it was or was not
17 osteonecrosis wasn't looked at by either of the two
18 reviews.

19 In other words, it was looked at only
20 radiologically, but not by looking at the slides.

21 DR. BUCKLEY: Do you want to --

22 DR. RAPPAPORT: I'll take that. Bob

1 Rappaport. We've gotten to the point today where
2 I'm going to try to clarify that in my charge to
3 the committee. But let me just say that, at this
4 point, I don't think we can parse it out that way.
5 We don't have the data. We don't have an adequate
6 time to look into this, and we really don't have
7 the kind of prospective data that we need to make
8 that assessment.

9 So what we're asking today is that you
10 consider all of those bad outcomes, and what we
11 want you to do is make the assessment based on the
12 incidence, frequency of bad outcomes in these
13 particular patient populations.

14 DR. BUCKLEY: Dr. Bilker, do you still have
15 a focused question for us?

16 DR. BILKER: Yes. I have one question for
17 Dr. Colburn. I wanted to ask, in the adjudication
18 of osteonecrosis, you mentioned that you considered
19 concomitant at-risk medications. What are the
20 classes of medications that put people at risk for
21 osteonecrosis, exclusive of NSAIDs?

22 DR. COLBURN: Certainly, we know that most

1 cases of osteonecrosis are associated with
2 corticosteroid use. That tends to be the most
3 frequent presentation that we see as clinicians
4 when a case presents to us with osteonecrosis.

5 Certainly, we see increased incidence of
6 osteonecrosis and certain co-morbidities, such as
7 the rheumatoid -- such as the lupus patient,
8 sometimes with a rheumatoid patient. But when I'm
9 thinking and I'm looking through these past medical
10 histories, I'm looking at the medications that
11 they're on at the time, what their past medical
12 history consists of, and I'm taking all of this
13 into account as I make my final adjudication
14 category.

15 I'd like to make it clear that when I did do
16 osteonecrosis, I considered all categories, primary
17 and secondary. But then I further broke that down
18 into the primary, the idiopathic, considered that
19 more so as an "other" diagnosis. But the
20 secondary, I kind of held on to because that would
21 be the case where, if there was a drug anti-NGF
22 association, that would be the clinical arena or

1 environmental milieu with which it would be
2 associated with. So it would be secondary
3 osteonecrosis.

4 Does that help clarify?

5 DR. BUCKLEY: Dr. Block, do you still have a
6 question?

7 DR. BLOCK: This is John Block. My question
8 is for Dr. Colburn, and I'd also appreciate
9 Dr. Bathon commenting on it. I think this is going
10 to mirror Dr. Kelly's comments earlier.

11 In my radiology practice, I see many
12 examples of advanced degenerative joint disease
13 without subchondral fracture. If you look hard
14 enough, you can see features of half a millimeter
15 of subchondral insufficiency fracture in many of
16 these patients. But in every example of imaging
17 that I've seen today attributed to the adverse
18 outcome, it has striking subchondral collapse.

19 So my question is, is that characteristic of
20 the entire adverse outcome group, or is it just the
21 images we've seen today? And if so, the
22 subchondral collapse, is that the event? And with

1 that being considered the sponsors' measurement of
2 joint space as an early indication of the adverse
3 event, is that an appropriate measure? Because
4 subchondral collapse is not associated with early
5 loss of joint space. That comes later as a result
6 of the incongruity of the joint surface.

7 DR. COLBURN: Yes. That's certainly a good
8 observation. And clinically, I just really feel
9 that there is probably this spectrum of events that
10 occurred. As I touched upon earlier, I think
11 that -- I feel, just seeing the trend, that
12 probably subchondral collapse or fracture was
13 probably the initiating event.

14 I'd like to defer to Dr. Bathon. But again,
15 it's difficult to make that. That's one of those
16 kind of clinical gestalt that you have when you
17 read -- when you see a lot of cases, you just see a
18 trend developing before you.

19 So again, I was at a disadvantage. I didn't
20 get to see the original films. I didn't really get
21 to see the original pathology. But some things
22 that I will take from this, and go back and look,

1 is I would like to look at those pathology and see
2 how many were associated with my diagnosis, and how
3 many actually had slides as opposed to actually had
4 readings.

5 I'd like to, again, look back at the imaging
6 and the imaging reading for these osteonecrosis and
7 see how many the sponsor kindly deferred and said,
8 "These are not correct readings," by the
9 radiologist that was sent to us initially. We have
10 yet another interpretation because we have now
11 looked at the original films, so therefore, we do
12 not think it was osteonecrosis.

13 I'm also interested as to why Pfizer in
14 particular -- when I think Janssen actually had an
15 adjudication of osteonecrosis, why Pfizer only
16 considered as one of their adjudication categories,
17 a priori, a category of primary osteonecrosis and
18 did not consider a separate adjudication category
19 termed secondary osteonecrosis.

20 DR. BUCKLEY: So Dr. Bathon, do you want to
21 comment? And then I think we probably have to end
22 the discussion of this question.

1 DR. BATHON: I think the whole issue of the
2 subchondral insufficiency fractures is fascinating.
3 I'm not a bone expert by any means. But remember,
4 we didn't have the original MRIs and we didn't take
5 stock in the local report of the MRIs at all
6 because, as Dr. Mont mentioned, if you saw
7 necrosis, it was often in descriptive terms with
8 osteoarthritis as well, so we didn't think that we
9 could use that term of necrosis.

10 They never mentioned fractures, as I recall.
11 But the Pfizer adjudication was very interesting
12 and they noted a lot of subchondral insufficiency
13 fractures. And though we didn't go back yet and
14 specifically try to correlate, I think that a lot
15 of the osteochondral defects that we're seeing
16 were, in fact, what was seen on the MRIs as
17 sufficiency fractures. And one has to wonder if
18 that was the primary insult. And it may suggest
19 that, perhaps, in ongoing studies, if they are to
20 take place, that maybe an MRI ought to be factored
21 into at least one of the joints, maybe looking for
22 those types of preliminary events.

1 DR. UPMALIS: Dr. Buckley, could I -- I'm
2 sorry.

3 DR. BUCKLEY: I'm sorry. We're way over
4 time. And I think there's a rich and interesting
5 discussion, but I don't think we have time for
6 that.

7 DR. UPMALIS: We do have a radiologist who
8 can speak to our evaluation.

9 DR. BUCKLEY: I understand, but I think
10 we're going to have to go on. This is the
11 committee's chance, and I think we need to make
12 sure they get heard.

13 DR. VERBURG: But nobody answered
14 Dr. Block's question about did that reference what
15 he saw today --

16 DR. BUCKLEY: But at this point, I'm going
17 to cut off the discussion, and I'm going to let
18 Dr. Mikuls ask his question.

19 DR. MIKULS: The conversation may continue a
20 little bit because it's a related question, and it
21 has to do with slide 67 that the FDA showed. And
22 it shows fractures. I may have missed it, but

1 anatomic sites of these fractures, are these all
2 the subchondral fractures we've been talking about?
3 Are these from reports? Are these from other
4 sides?

5 Primarily what drove this question was some
6 of the animal data that was presented showing
7 osteoclast biomarker increased, particularly with
8 the combination of NSAID and study drug.

9 So I'm curious what we know about these
10 fractures, because I didn't hear really what they
11 were.

12 DR. HERTZ: So these were fractures that
13 were not specifically just subchondral. These were
14 all fractures that were reported.

15 DR. MIKULS: That's not very helpful. So
16 are they vertebral fractures? What numbers are
17 they? Were they reported? Or maybe they're not
18 characterized further than that?

19 DR. HERTZ: Yes. We don't have those
20 details in the data that was available. In the
21 table of data that we got listing adverse events by
22 treatment group, we were looking at things that

1 were higher in the active than in the comparators,
2 and one of the things that showed up were these
3 fractures. And what was interesting was that they
4 were both traumatic, and then we saw some that were
5 non-traumatic.

6 DR. MIKULS: So not to beat the dead horse,
7 but not very helpful at all --

8 DR. HERTZ: It is what it is.

9 DR. MIKULS: To help us think through this
10 very, very important question, that's not very
11 helpful. If this is all muddled with subchondral
12 fracture that's part of this bad process, that's
13 another thing. But if these are separate fractures
14 suggestive of more global bone effect, we'd want to
15 know that.

16 DR. BUCKLEY: So a lot of information, a lot
17 of information to process. But I think we're going
18 stop here and move on to the discussion period and
19 to the questions.

20 First, I'd like to introduce Dr. Rappaport.
21 He is going to charge the committee with the issues
22 and answers he wants us to deal with.

Charge to the Committee

DR. RAPPAPORT: So at this time, I'm going to ask you to consider all of the data that you've heard today, the additional commentary, and opinions, and what was in the background packages, and to begin your discussions related to our specific questions.

Please note that the discussions at a committee meeting like this are generally far more helpful than a simple yes/no vote on the questions that we pose to you. The issues that we bring before you are just never very simple and always require some degree of judgment, based not only on expertise, but also on the wisdom that comes with a lot of experience. It's, therefore, extremely important that you share with us, to whatever degree possible, your thought processes leading up to the conclusions and recommendations.

Today's challenge is a particularly difficult one. There are patients with severe chronic pain for whom the available analgesic products are either ineffective or poorly

1 tolerated, and we'd all like to find new analgesics
2 to help those patients. But it's also essential to
3 ensure that the benefits of any product clearly
4 outweigh its risks for the intended population, and
5 in this case in particular for the patients, and
6 the subjects, and the studies.

7 Perhaps there is a path forward to safely
8 study the anti-nerve growth factor agents. And
9 clearly, that's what we're all trying to sort out,
10 though the evidence is confusing at this point. I
11 think that's become apparent by this time of the
12 day.

13 We're just beginning to explore what's the
14 relationship with not just exposure to these
15 agents, but also their concomitant use with NSAIDs.
16 And we're beginning to explore the underlying
17 pathophysiology. It's not well understood. But
18 for today, I would say to you that these are not
19 essential to assessing the path forward.

20 We wanted to give you some opportunity to
21 discuss those issues, to discuss whether you could
22 tease out a diagnosis or understand the

1 pathophysiology and the cause of these events. But
2 not believing that that really was going to be an
3 outcome today, we're early enough in development
4 that we will need additional study, I think, if
5 we're going to get those answers. For now, what we
6 need is your help to define what the path forward
7 might be for getting additional information.

8 These events are severe. Whatever we call
9 them, whatever they turn out to be, and whatever
10 the underlying process is, they're severe, and they
11 seem to be occurring in relationship to exposure to
12 these agents. And you should start from there.

13 No doubt, if development continues through
14 to a marketing application, if we can get that far,
15 we will be bringing these agents back to you for
16 more discussion. And I can assure you that the
17 sponsors will be doing everything they can to
18 define better what's going on here because,
19 ultimately, they're in competition with each other,
20 and they want to be able to say, ours is safer
21 because, or ours is more effective because. So
22 they have a great incentive to look deep into this

1 and really understand what's going on here. And we
2 have an incentive to try to have these better
3 understood so that we can get them out to the
4 patient population if it's appropriate. So we will
5 be bringing them back if we can get them moving in
6 this process.

7 We hope that, at that point, we'll have that
8 additional clarity regarding both the
9 pathophysiology and the diagnoses, and how these
10 events are actually occurring. But at this point,
11 we don't; so if you could focus on knowing that
12 these events are occurring, they're very bad, and
13 they're occurring in association with exposure to
14 these agents.

15 The question is, how can we move forward and
16 can we move forward, and if so, how. And I thank
17 you for taking that challenge on.

18 **Questions to the Committee**

19 **Committee Discussion**

20 DR. BUCKLEY: So we will now proceed to the
21 questions to the committee and the panel
22 discussion. I'd like to remind public observers at

1 this meeting that while this meeting is open for
2 public observation, public attendees may not
3 participate except at the specific request of the
4 panel. We have a number of discussion questions,
5 and we have a few voting questions.

6 Just to go over the voting process, for the
7 voting questions, we'll be using the electronic
8 voting system for this meeting. Each of you has
9 three voting buttons on the base of your
10 microphone, yes, no, and abstain. Once we begin
11 the vote, the buttons will start flashing and will
12 continue to flash even after you've entered your
13 vote. Please press the button that corresponds to
14 your vote. If you're unsure of your vote or you
15 wish to change your vote, you may press the
16 corresponding button until the vote is closed. The
17 vote will then be displayed on the screen.

18 The DFO will read the vote from the screen
19 into the record. Next, we will go around the room,
20 and each individual who voted will state their name
21 and their vote into the record. You can also state
22 the reason why you voted as you did if you want to.

1 We will continue in the same manner until all the
2 questions have been answered or discussed.

3 So we're going to start the discussion
4 around the first question, which you have in your
5 booklets, and that's number 1. And that discussion
6 point is, the data presented today describe a
7 safety signal in clinical studies of anti-nerve
8 growth factor agents that are under development for
9 the treatment of pain due to a variety of
10 disorders.

11 Please discuss whether these adverse events
12 of painful and rapid joint destruction are
13 occurring with an unusually high incidence in the
14 population studied and/or are unusually severe
15 compared to joint-related events that occur in this
16 population.

17 Now, we've spoken around this issue, but
18 rather than clarifying, this is the time for us to
19 give opinions. And again, we will recognize people
20 in the order in which they would like to speak.

21 Dr. Kelly?

22 DR. KELLY: Speaking just from my 21 years

1 as a knee surgeon, I think these events are
2 extraordinarily high and severe.

3 DR. BUCKLEY: Thank you.

4 Dr. Haque?

5 DR. HAQUE: Mustafa Haque. I also agree
6 that these are fairly high rates of incidence and
7 far more severe than we see with other types of
8 treatments for OA.

9 DR. BUCKLEY: Dr. Block?

10 DR. BLOCK: This is John Block. The
11 radiographic features are fairly unique in that the
12 degenerative joint change is accompanied with
13 relatively little sclerosis or bone formation. The
14 margins of the joint and the subluxations are
15 fairly unusual, so I would say that this is a
16 unique outcome.

17 DR. BUCKLEY: Dr. Lahita?

18 DR. LAHITA: I also agree that these are a
19 unique group of safety signals. I'm a little bit
20 confused about osteonecrosis, which I think is the
21 most severe aspect of it, but I think this rapid
22 progressive osteoarthritis is significant. Whether

1 we should or should not qualify some of this, I
2 think I'll leave for a moment.

3 DR. BUCKLEY: Yes. Dr. Morrato?

4 DR. MORRATO: Yes. Elaine Morrato. I'd
5 just like to add the point that the FDA had in
6 their briefing materials, that some cases occurred
7 in patients without a history of OA, which would
8 further support the significance of the findings.

9 DR. BUCKLEY: Anyone else might want to make
10 a statement about this?

11 [No response.]

12 DR. BUCKLEY: So to summarize, I think to
13 the FDA, there's, in general, agreement in the
14 group that these events are occurring, that they
15 are not the classic OA pattern that we would expect
16 to see in this population, that there's various
17 names given to them, that the pathology isn't
18 completely worked out. Osteonecrosis may be part
19 of this pathology in some patients and not in
20 others. And there's a concern that this is
21 happening in a patient without history of
22 osteoarthritis.

1 So I think, in general, there's concern that
2 this is a distinct event, and that it's an event
3 with a significant negative outcome.

4 Does that address that question for you?

5 We're going to move on to the discussion
6 point number 2. This is a long one. I think we've
7 addressed some of these points, but I'm going to
8 read through them and see if there's any other
9 comments we might want to add or which areas we
10 want to address.

11 Do you agree with the sponsor's
12 interpretation of the data which states that
13 rapidly progressive OA has been identified as a
14 safety signal in the tanezumab and fulranumab
15 clinical programs; that osteonecrosis does not
16 represent a safety signal; that rapidly progressive
17 osteoarthritis type 2 is a relatively distinct
18 finding in the tanezumab studies? And I think, by
19 distinct, the FDA means it's a new or different
20 finding than what we're used to seeing.

21 Anti-NGF agents may represent an advantage
22 in terms of efficacy, so we'll speak I think in

1 this session a little bit about the therapeutic
2 advantage over other analgesics for the treatment
3 of osteoarthritis and painful conditions, so
4 efficacy and degree of efficacy.

5 The risk-benefit profile of tanezumab
6 monotherapy and the treatment of OA is favorable
7 compared to treatment with placebo, non-steroidal
8 anti-inflammatory drugs, or extended-release
9 oxycodone.

10 The risk-benefit profile of tanezumab/NSAID
11 combination therapy is unfavorable compared to
12 NSAID treatment alone and to tanezumab monotherapy.

13 The data suggests that many events were
14 pre-existing or associated with the subchondral
15 insufficiency fracture of the knee or atrophic knee
16 OA of the hip.

17 Is NSAID use up to 90 days safe? Did it not
18 elevate risk?

19 Finally, the data suggests that a possible
20 mechanism for the safety signal is an increased
21 load on a susceptible joint or the presence of pain
22 relief.

1 So we'll start an open discussion and again,
2 a show of hands. Dr. Clemens, we'll start with
3 you.

4 DR. CLEMENS: I mean, I had this comment
5 earlier. Not all of these antibodies are
6 presumably the same and have different kinetics,
7 and so forth. So some of these questions may be
8 specific to one or the other.

9 For example, B, osteonecrosis does not
10 represent a safety signal. I mean, isn't it true
11 that they can't all be assumed to be the same
12 exact -- I mean, the mechanism is presumably the
13 same, but can the half-life, the on-off, and so
14 forth be considered the same? I didn't hear that
15 discussed.

16 DR. BUCKLEY: Are you saying that the answer
17 to these questions may differ by agent or differ
18 within a patient given an agent?

19 DR. CLEMENS: Yes. We haven't heard much
20 about -- I mean, the antibodies work the same way
21 presumably, but not all antibodies are the same,
22 and the kinetics are different, and they may

1 produce slightly different effects.

2 So we can we answer like question B for all
3 the agents?

4 DR. BUCKLEY: I presume you're asking us to
5 give more generic answers, given the limitations of
6 what we know between the differences in these
7 agents.

8 DR. RAPPAPORT: Yes. But if you can't
9 answer at this point because the data are
10 insufficient, that's okay and that's something we
11 want to hear from you.

12 DR. BUCKLEY: Dr. Suarez?

13 DR. SUAREZ-ALMAZOR: Yes. I had a couple of
14 comments with respect to the several points that
15 are here. The first one is related to the
16 efficacy. I would say that, at most, the efficacy
17 is just modest. It's only a 10 percent difference
18 with NSAIDs, so if we are to evaluate the
19 risk-benefit profile, the benefit seems to be very
20 modest at most. As we said before, the NNT is 10,
21 so we would need to treat 10 patients just to have
22 benefit in 1, compared to what we can achieve with

1 NSAIDs, so that's my first point.

2 Then I have to say that I disagree with the
3 conclusion, with point I, that says the data
4 suggests that a possible mechanism for the safety
5 signal is an increased load on a susceptible joint
6 in the presence of pain relief. I mean, people run
7 marathons and they don't destroy their joints in
8 such a way, so I really disagree with that
9 conclusion at the end.

10 DR. BUCKLEY: Dr. Gabriel?

11 DR. GABRIEL: Sherine Gabriel. I'll just
12 make a couple of points here. With respect to B,
13 osteonecrosis does not represent a safety signal, I
14 disagree with that. I think there is really
15 inadequate information to agree with a negative
16 statement as stated.

17 In 87 cases, the treating physician thought
18 it was osteonecrosis. With respect to the FDA
19 report and Dr. Bathon's report, there's uncertainty
20 about that or perhaps there is a diagnosis. So I
21 certainly cannot agree with that statement.

22 Like Dr. Suarez-Almazor, I really don't

1 think there is evidence to support statement I,
2 either, that the mechanism is a function of pain
3 relief.

4 DR. BUCKLEY: Thank you.

5 Dr. Kelly?

6 DR. KELLY: I will just echo to maybe the
7 more provocative, number 8 -- or G; excuse me. I
8 think that pre-existing subchondral insufficiency
9 is not the case because if that were, then there
10 would not be an increase over just NSAIDs alone.
11 That assumes that there happened to be more in one
12 group when I think the randomization would argue
13 otherwise.

14 I agree with the other panelists that, for
15 I, with the fragmentation, the subchondral
16 collapse, the osteoporosis, I think there may be
17 some hyperemic effect analogous to Charcot joints.
18 So it's more than just innervation.

19 DR. BUCKLEY: Dr. Khurana?

20 DR. KHURANA: Jasvir Khurana. I think the
21 first three points are a little muddy. The FDA did
22 not actually look at films and histology, so the

1 mechanism subchondral fracture versus
2 osteonecrosis, et cetera, I think are not easily
3 answerable.

4 For the fourth point -- if I could have that
5 point number 4 -- whether there is an advantage
6 over other analgesics for the treatment of
7 osteoarthritis and other painful conditions, I
8 think a lot of the other painful conditions were
9 not well looked at, endometriosis, post-herpetic
10 neuralgia, et cetera. So I think there's just not
11 a lot of data on that.

12 DR. BUCKLEY: Dr. Bothwell? Dr. Morrato?

13 DR. MORRATO: Yes. Elaine Morrato. I
14 wanted to provide comment on H, which is, "The
15 NSAID use up to 90 days did not elevate risk." And
16 I don't think that we can necessarily conclude that
17 from the data that was presented. It's
18 interesting, and I would agree with the goal of
19 providing clear instructions to inform patient
20 care, but we were limited, I think, in sample size.
21 We really only saw data, I believe, from the
22 tanezumab. And it wasn't well discussed how well

1 NSAID use was actually captured in the drug-use
2 records, particularly around over-the-counter drug
3 use, duration, and so forth.

4 So it's an interesting set of analyses, but
5 I don't think it's definitive to make this
6 conclusion.

7 DR. BUCKLEY: Thank you.

8 Dr. Gerstenfeld?

9 DR. GERSTENFELD: I would like to concur
10 with the conclusion about I, that I don't think any
11 data was presented that would support the idea that
12 increased use would lead to a consequence of the
13 disease.

14 I also agree with the issue that the current
15 review of the data doesn't -- without primary
16 pathology, you can't determine what the underlying
17 etiology was, whether it's osteonecrosis or
18 subchondral damage. So I think you really need
19 more data.

20 Then as a class effect, I think that you
21 would have to survey all joints upon entry into
22 study before you can conclude a relationship to

1 different treatment effects. So those are my
2 comments.

3 DR. BUCKLEY: Ms. Cowan?

4 MS. COWAN: My concern is -- I mean, there's
5 a lot I think missing information here, and I think
6 the biggest concern for me is the fact that the
7 original x-rays and graphs were not provided to the
8 FDA, and I'm not sure why. I mean, that makes me
9 uncomfortable, especially when the other
10 adjudicators had that information.

11 So I mean, overall, I just think that
12 there's a lot of missing information here that
13 makes me very uncomfortable.

14 DR. BUCKLEY: Thank you.

15 Dr. Haque?

16 DR. HAQUE: I think the one thing that I can
17 strongly agree with is F, that the combination of
18 the tanezumab and NSAIDs was pretty clearly a big
19 risk factor over baseline NSAID or tanezumab.

20 DR. BUCKLEY: Thank you.

21 Dr. Neaton?

22 DR. NEATON: Actually, I was going to say

1 the same thing as Dr. Haque. The only statement
2 here that I agree with, without qualification, is
3 F. It seems like clearly there the combination is
4 more unfavorable. I think there's a lot more
5 uncertainty about the different drugs from the
6 three sponsors versus placebo and versus another
7 active comparator, and even more uncertainty yet
8 about the dose response.

9 I'm not convinced that even at low doses,
10 there's not a signal. And particularly, I think a
11 concern that I have is with longer follow-up and
12 kind of more in keeping with how these drugs would
13 be used, we're maybe missing something. And we
14 don't know that from this information, and you
15 won't know that unless you do a study. But I think
16 that's a concern.

17 DR. BUCKLEY: Thank you.

18 Dr. Neogi?

19 DR. NEOGI: I agree that the first three
20 points about the radiographic appearance and
21 pathology is unclear. And I feel that there has
22 been inadequate data with the different definitions

1 used and not everyone having access to the same
2 original films and slides.

3 I agree that the last point, the mechanism
4 about increasing load, while attractive, we haven't
5 seen any data to support that. Point G, that many
6 events were pre-existing or associated with a
7 subchondral insufficiency fracture, I don't think
8 we can say that many events fall into that category
9 since not all joints were necessarily
10 systematically evaluated at baseline to know this.

11 In terms of efficacy, I do want to say that
12 I think there is a tremendous unmet need, as has
13 been said, stated here previously. And for
14 patients that can't take NSAIDs, or opiates,
15 et cetera, I think this is something that I would
16 hesitate to just throw it away because of these
17 concerns. I think we need a better understanding
18 of how to risk-stratify the patients and the
19 treatment strategies to enable this to move
20 forward.

21 DR. BUCKLEY: Ms. Broyles?

22 MS. BROYLES: Hi, Susan Broyles, patient

1 representative from Fort Worth. And I guess I'm
2 trying to look at this, first of all, as a patient,
3 but certainly not just from a personal, but I'm
4 also an oncology nurse for over 25 years and an
5 intractable pain patient now for 10 years, although
6 that's more of a neuropathy situation.

7 But I see this as being dealt with pain as a
8 whole. And I think on a day-to-day basis, when you
9 deal with that, certainly, if you find something
10 that works, then you're blessed. And if you're
11 not, it's usually ongoing, up and down, and
12 switching things. And it's such a complex thing to
13 treat because it's not just the physical pain.
14 There are so many things that are associated with
15 it that make that part worse.

16 But to close the door -- because one thing's
17 for sure. Pain's not going to go away, and it's
18 still going to be here, and there's going to be
19 different tolerances and dependence in this. And I
20 think there are so many things that still need to
21 be recognized and accepted about the whole pain
22 thing, and to just rule something out -- but there

1 are very serious, devastating-type consequences in
2 some situations, but as to some of the others, we
3 don't know enough yet about.

4 But it's a day-to-day deal. And the cancer
5 patient population in particular, I mean, I see
6 that hadn't been referred to, where they're still
7 treating those as though it doesn't matter, they're
8 going to die anyway, almost, to some degree. But
9 those patients are excellent resources for pain
10 because they have a select type of pain, but at the
11 same time, because of their limited situation or
12 their treatments they're going through, they truly
13 are good resources for that and to follow up with
14 as far as their results.

15 DR. BUCKLEY: Thank you.

16 Dr. Lahita?

17 DR. LAHITA: Dr. Lahita from New Jersey. I
18 agree with the previous speaker. One item here is
19 we tend to emphasize at this proceeding
20 osteoarthritis, but there are other painful
21 conditions. And as chairman of medicine of a large
22 hospital, one of our issues is the management of

1 cancer. In stage 4, very severe cancer pain, I
2 don't think this should be thrown out is what I'm
3 saying. Cancer is a major issue. And something
4 that's not been mentioned, which is a major problem
5 in the urban environment, is sickle cell crisis,
6 where my house staff prescribes, I would say,
7 pounds of opiates each month for patients with
8 sickle cell disease alone.

9 Then with regard to E, the risk-benefit
10 profile of tanezumab monotherapy and the treatment
11 of OA is favorable compared to treatment with
12 placebo, well, I again do not want to throw this
13 out, but oxycodone happens to be one of the most
14 abused drugs in our society. And there is a new
15 oxycodone that's coming out, that is 10 times more
16 potent than the one we currently have. This is a
17 social problem. So if we can minimize the use of
18 opiates with a new agent, which is applicable to
19 severe kinds of pain, I think this would be very,
20 very appropriate.

21 DR. BUCKLEY: Dr. Mikuls?

22 DR. MIKULS: Yes. I guess I'd just like to

1 echo that comment and that we all in rheumatic care
2 struggle on a day-to-day basis with helping our
3 patients with pain. I think having a novel agent
4 that works in a different pathway is critically
5 important.

6 The key moving forward, clearly, is risk
7 mitigation and how we can minimize the number of
8 patients who have these awful adverse effects. And
9 I think the FDA, as an advisor I'd say, you need to
10 be utterly comfortable with the data in regards to
11 risk mitigation, that we can indeed mitigate
12 90 percent of the risk by avoiding patient A, B,
13 and C that was presented earlier. I didn't see
14 that from the FDA, and it would be nice to see.

15 DR. RAPPAPORT: I'm not sure that's
16 something that we can really do. I mean, we were
17 sort of hoping that you folks who have a lot more
18 expertise than we do would be able to look at that
19 and make more sense of it. And you can cut the
20 data any way you want and come up with both
21 arguments, I think.

22 DR. MIKULS: I think it could be done. I

1 mean, I think the data is there, and you could do
2 sensitivity analyses to get an idea of which of
3 those cases truly could have been avoided.

4 I will leave here, I suspect, not super
5 comfortable with the numbers that were provided, I
6 mean, because -- you really need to go through that
7 and cut it many different ways, as you said, to
8 feel comfortable with that.

9 DR. BUCKLEY: Dr. Blumenthal?

10 DR. BLUMENTHAL: This is Blumenthal. Well,
11 this is certainly very complex. And I think one of
12 the problems we're grappling with here is the
13 quality of the data. And the reason we're having
14 problems with the quality of the data is because
15 the pre-clinical studies did not indicate that we
16 needed to have concerns about rapidly progressive
17 osteoarthritis, that we needed to have concerns
18 about the health of subchondral bone, or that we
19 needed to have concerns about joints other than the
20 index joint.

21 So now, we're doing sort of a post hoc
22 retrospective analysis, trying to reconstruct what

1 the heck happened in these patients who appear to
2 have had bad outcomes. And we're struggling to do
3 that because we don't know the pace of the
4 progression of the native disease when you get a
5 radiograph somewhere between one month and nine
6 months prior to enrollment. And then at some time
7 point later, you don't know, really -- have any
8 sense of how rapidly their native disease was
9 progressing prior to the study. And you're trying
10 to speculate about it after the fact. Not having
11 any idea that there was going to be problems in
12 index joints, in joints other than the index joint,
13 means sometimes, we have no imaging data at all
14 about these non-index joints.

15 So now we're being asked to render a
16 judgment about this class of medications in an
17 environment where we're all struggling with the
18 inadequacy of the data. And I suppose one of the
19 ways to look at this is to say that there is
20 sufficient evidence of harm, that we continue this
21 sort of moratorium on research with these agents,
22 or that we decide that we just kind of have to

1 start over, as if there had been a dangerous signal
2 in the pre-clinical studies, and that the clinical
3 studies just have to be re-done with different
4 enrollment criteria, different data points that are
5 obtained prior to the start of the study, more
6 rigorous observation of index and non-index joints
7 as the study unfolds, a greater awareness of the
8 NSAID issue that might also exist here.

9 Because this is not going to be the end of
10 this, in my opinion. If you extrapolate from the
11 rheumatoid arthritis experience, we're at the start
12 of something that's going to go on through many
13 iterations for many years.

14 First, we have the monoclonal antibody that
15 recognizes the native molecule. Then we have the
16 monoclonal antibody that recognizes one or more of
17 the receptors. Then we have the monoclonal
18 antibodies that interfere with the action of
19 certain biologic effects of the original molecule,
20 but not with other biologic effects, and having
21 disparate effects on certain neurotrophic factors
22 compared to others. Then natural antagonists are

1 found, where they would be natural to the human
2 body, but they are counter-regulatory molecules
3 that interfere with these biologic functions of
4 nerve growth factors. And then there are tyrosine
5 kinase inhibitors that work on the signaling that
6 is downstream from the receptors that are at play
7 here.

8 So each time somebody proposes a molecule of
9 that sort, they're going to file an investigational
10 new drug application, and they will argue that it's
11 not the same as these anti-TFF antibodies because
12 of this, and this, and this.

13 So we have to have all these safety measures
14 in place for all of those proposed investigational
15 new drugs. And when you look back on it, then,
16 from that perspective, do the people who develop
17 this very first agent, are they excluded from
18 having their drug under consideration just because
19 nobody knew it was going to turn into this big
20 mess? But the people with brand new drugs, they
21 get to go ahead and have their studies? It's very
22 complicated.

1 So I suppose one of the possibilities here,
2 if the FDA and the sponsors were agreeable, is to
3 kind of start over. I'm really serious about this,
4 knowing what we know now and taking another look at
5 this in a way that attempts to maximize patient
6 safety for any enrollees in the study. And they
7 will absolutely have to have full informed consent,
8 where they essentially know what we know before
9 they sign up for any such study.

10 That's all I have to say.

11 DR. BUCKLEY: Thank you.

12 Dr. Boyce?

13 DR. BOYCE: I just wanted to express my
14 concern about the short period of time that the FDA
15 and their external advisor had to review what must
16 have been a ton of data. And I'm not really sure
17 why we're here today, hearing their opinions on
18 this when they're being limited by unavailability
19 of these data. So I find it difficult to support
20 many of the claims that the sponsors have made
21 here.

22 I think it's also important that we

1 understand that not all drugs in the same class
2 work in exactly the same way. They may bind to a
3 protein and stop it interacting with each receptor,
4 but I know there are various different TNF
5 inhibitors. And some might work for one patient
6 and some may not. And it's a case of flipping
7 among TNF inhibitors in patients with rheumatoid
8 arthritis to figure out which one may work for
9 them.

10 So I would support Dr. Clemens' concerns
11 that there may be, among these three agents, one of
12 them that may be better than the other two, or two
13 of them may be better than one.

14 DR. BUCKLEY: Thank you.

15 Dr. Rappaport?

16 DR. RAPPAPORT: Yes. Let me address both
17 Dr. Boyce and Dr. Blumenthal's comments. First of
18 all, we had to balance out how long we were willing
19 to take to review the data, which was of limited
20 quality to begin with because it is retrospective,
21 with holding up the development program for three
22 drugs that were in phase 2 development. And we're

1 talking about, you know, a significant problem for
2 industry by doing that and potentially holding up
3 an important drug. We don't know.

4 Somewhere, we had to make a cut and say,
5 this is as much as we can do right now. And even
6 if we spent another 6 or 12 months looking at this
7 and held up these development plans for another 6
8 or 12 months, we may not have much more useful
9 information to provide to the committee.

10 So that's an answer to your comment.

11 I would encourage the committee to go down
12 the path that Dr. Blumenthal has laid out and start
13 thinking about exactly what it is that we need to
14 understand and whether we need to go back to square
15 one, or square two, or square three to study these
16 drugs.

17 You said, should we hold these sponsors who
18 have already studied them to different standards
19 than somebody else who might come in with a
20 slightly different product. No, of course not.
21 Everybody should be going back and looking at the
22 things that haven't been looked at because we

1 didn't expect them the first time around.

2 So I think the discussion that would be very
3 helpful to us is, how far back do we need to go?
4 What safety monitoring? What evaluations should be
5 done in order to let studies proceed and in what
6 patient populations?

7 DR. BUCKLEY: Dr. Rappaport, do you want us
8 to go ahead and summarize this area, and then move
9 on to the suggestions for where to move forward?
10 Or do you want to deal with that as we move further
11 through the discussion?

12 DR. RAPPAPORT: If people feel they've had
13 an adequate chance to express themselves, that's
14 fine. It's up to you. It's your call.

15 DR. BUCKLEY: So we have a couple more
16 speakers on the list, Ms. Cowan, Dr. Neaton, and
17 Ms. Broyles.

18 Anyone else want to deal specifically with
19 these issues? Ms. Cowan, do you want to speak
20 specifically to this?

21 MS. COWAN: Yes. Especially what I've been
22 hearing because, I mean, we started out with

1 116 million people, we heard, that are living with
2 chronic pain. We also heard, "do no harm." And
3 while I said I'm very concerned about the missing
4 data and not the original films, I think there's a
5 grain of hope there. I also represent people with
6 pain. And I think that we need to think about that
7 and realize that they'll do anything to get out of
8 pain.

9 What I'm concerned about is a longer-term
10 follow-up, more informed consent from some of the
11 letters that I've read. I think we need to look at
12 it and be more careful. I don't want to throw it
13 away. That's all I wanted to say.

14 DR. BUCKLEY: Dr. Neaton, do you want to
15 address this specifically? No. Okay.

16 Ms. Broyles?

17 MS. BROYLES: I just wanted to add, when we
18 were going down the list, particularly with the
19 long-acting opioids, the oxycodone for example, I
20 think over -- certainly in the last 10 years,
21 things have improved considerably. And there's a
22 big issue with opiate abuse, no doubt. And then

1 there comes dependence versus addiction. And I've
2 learned all this because I've had no choice. But
3 it's been a big learning experience, but it's all
4 about turning that signal off in the brain. And
5 what works for one person -- in oncology, we always
6 say the right dose of medicine is the one that
7 works.

8 So I think with non-cancer pain and
9 certainly in these studies, the primary focus has
10 been osteoarthritis. And maybe before we spread
11 out to all these others, figure out where things
12 are going wrong there, because that is a huge
13 population of patients. But just to say the other
14 medications that have been under view -- I mean,
15 because some of the long-acting drugs have
16 literally given people enough of a life to be able
17 to function, and go to work every day, and have a
18 family, whereas when they were taking something
19 every three hours -- because there is something to
20 that long-acting benefit of any of the drugs. And
21 with the opioids, at least we know where we are
22 with those as far as side effects. I mean, you're

1 going to have this, and this, and this. But once
2 you have a tolerance, we know -- we doubt that one
3 of your joints is going to come into play.

4 So it's always probably going to end up
5 being a combination of things to block the
6 receptors and turn that signal off. That's all.

7 DR. BUCKLEY: Thank you. Thank you very
8 much.

9 So just to conclude this question, I have
10 Dr. Kelly down. Do you still want to speak? We're
11 going to move on to address what next.

12 DR. KELLY: Yes. Just a summary for my
13 viewpoint on the efficacy, I know I've trashed
14 certain elements of this, but I have to concur or
15 concede that we can't throw the baby out with the
16 bathwater. There was one slide that oxycodone was
17 no better than placebo. I spent half my day
18 talking people out of narcotics. I think that, to
19 me, what gives me the heebie-jeebies is the
20 vehicle.

21 Anything IV gives me the heebie-jeebies. So
22 maybe the vehicle could be the answer, slow

1 release, more focally administered. Of all the
2 things presented today, the thing that really
3 disturbs me the most is the remote-site arthritis
4 progression of joints that had no native OA.
5 That's worrisome. However, if this could be
6 crafted to more of a locally administered,
7 timely -- there is a potential niche that have many
8 patients that aren't surgical candidates that could
9 benefit from this.

10 So I don't think we should totally dismiss
11 this as a potential promising agent.

12 DR. BUCKLEY: Thank you.

13 And Dr. Khurana, do you want to add
14 something?

15 DR. KHURANA: Sorry. Yes. I will try and
16 be really quick. With respect to what
17 Dr. Blumenthal said, essentially, if were going to
18 start again, would you want to look at data
19 including osteoarthritis patients or limit this to
20 patients with other forms of illness, cancer and so
21 forth?

22 DR. BUCKLEY: Thank you. And I think we're

1 going to get to that with the next question as
2 well.

3 So to briefly summarize discussion point 2,
4 I think, as far as point A, whether you call it
5 rapidly progressive osteoarthritis, some
6 destructive joint event, I think we agree, is going
7 on. I think the committee feels there is
8 osteonecrosis, but the exact pathological mechanism
9 of that -- and if there is more than one mechanism
10 is somewhat unclear. And the data on
11 osteonecrosis, we don't have enough yet. We've
12 talked about this being a distinct finding, and I
13 think, in general, the committee agrees.

14 I think everybody around the table has
15 talked about the need for new analgesic medicines,
16 and I think there is concurrence that there might
17 be some potential. Some members of the committee
18 are concerned that the effect is modest, or perhaps
19 at the level we're getting the effect, we begin to
20 get more toxicity. But I don't think anybody or
21 not many people want to say, "Let's just give up
22 this class of agents," at this point. Many feel

1 there's not enough data.

2 The hard question, I think, is either risk-
3 benefit profile, because we don't have enough data
4 to know completely, but I think there has been some
5 consensus that the risks of the currently available
6 agents, NSAIDs and opioids, is very high. This
7 agent probably has risks as well, but given that
8 the other agents do, it wouldn't preclude it, I
9 think, from moving forward in further study.
10 There's an agreement that NSAIDs appear to add to
11 the toxicity and that these events seem to occur in
12 pre-existing OA joints, but also in joints that
13 were not affected by OA.

14 I think, in general, the committee is
15 uncomfortable that we know what the threshold is
16 for NSAID use, that we just don't feel like we have
17 enough data. And I think some concern has been
18 voiced that given the propensity of NSAID use in
19 the community and that people use NSAIDs without
20 necessarily knowing their NSAIDs, that whether this
21 is in a trial or actually in clinical use, it's
22 going to be challenging if NSAIDs add to toxicity,

1 so not just in the clinical trial, but when we go
2 out into the community.

3 The mechanism of the safety signal I think
4 is an interesting one. And I think the group has
5 felt they don't have enough information to know
6 that completely. There is data that suggests
7 perhaps it's due to the analgesic effect and maybe
8 overloading or mechanical stress. But I think
9 there's also concerns there may be other effects
10 that we don't know yet. We don't have enough data.

11 Dr. Rappaport, does that answer your
12 questions for discussion point 2?

13 DR. RAPPAPORT: Yes. Thank you.

14 DR. BUCKLEY: So a deep breath, and we'll
15 move on to discussion point 3. Anti-NGF agents
16 have been studied in a variety of conditions and
17 represent very large populations, such as
18 osteoarthritis and low back pain, with a number of
19 approved therapies and also in smaller populations
20 that lack effective therapies, such as interstitial
21 cystitis.

22 Considering what is known thus far about the

1 risks and benefits associated with this class of
2 biologic agents, are there any populations for
3 which further clinical development would be
4 acceptable? If yes, discuss which specific patient
5 populations/painful conditions may be appropriate
6 for further study as defined below.

7 So we'll open this for discussion.

8 Dr. Lahita has mentioned sickle cell disease. And
9 we'll take hands to see if there's other thoughts
10 from members of the committee.

11 Dr. Clemens?

12 DR. CLEMENS: Was the question whether it
13 might be used for sickle cell?

14 DR. BUCKLEY: Dr. Lahita brought up before
15 that he thought a population that might be
16 interesting to look at for this agent.

17 DR. CLEMENS: That predisposes to
18 osteonecrosis.

19 DR. BUCKLEY: I know. Yes. That is a
20 concern.

21 DR. LAHITA: Can I just address that? Yes.
22 You're absolutely correct. That was why my concern

1 about osteonecrosis was paramount. You're
2 absolutely correct. But that's a young population
3 who are heavily dependent on morphine, opioids,
4 dilaudid, ID, Benadryl to enhance dilaudid,
5 et cetera. It is a major medical problem in the
6 urban setting.

7 DR. BUCKLEY: Dr. Clemens, any other
8 comment?

9 DR. CLEMENS: No.

10 DR. BUCKLEY: Dr. Haque?

11 DR. HAQUE: I don't treat sickle cell all
12 that often, but the ones that I've seen, I've
13 treated for osteonecrosis of shoulders and other
14 joints. And that would not be a population that I
15 would feel all that happy giving this medication
16 to.

17 DR. BUCKLEY: Any other suggestions to the
18 FDA for painful conditions that this agent might be
19 considered for?

20 DR. LAHITA: Metastatic carcinoma, breast
21 carcinoma, lung carcinoma to bone, breast to bone,
22 et cetera. I'm sure that the least of these

1 patients' worries are osteonecrosis.

2 DR. BUCKLEY: Dr. Kelly?

3 DR. KELLY: I'm just going to wear my sports
4 hat. There are a certain subset of extreme
5 tendinopathies that's been shown to be related to
6 neuronal sprouting, so non-operative older folks
7 with end-stage tendinopathies, painful.

8 DR. BUCKLEY: Dr. Rappaport?

9 DR. RAPPAPORT: You could also be more
10 general in answering this question, in saying
11 that -- without having to go into specific
12 disorders that maybe you're not as familiar with,
13 such as interstitial cystitis, you might say that
14 people who have refractory painful conditions or
15 who are terminal -- I mean, you can use more
16 general terminology to address this question and
17 the discussion.

18 DR. BUCKLEY: Dr. Boyce?

19 DR. BOYCE: I, too, thought of metastatic
20 bone disease as one of the indications for this,
21 but one of the standard treatments today, in
22 addition to chemotherapy, is intravenous

1 bisphosphonates and nerve intravenous tanezumab.
2 And these have both been linked to osteonecrosis of
3 the jaw, which is a severely debilitating condition
4 in patients with poor dental hygiene. So a
5 cautionary note would have to be in there about
6 giving something which may cause osteonecrosis
7 elsewhere.

8 DR. BUCKLEY: It seems that it might also be
9 appropriate to look at these agents in disorders
10 that seem to be primarily neurally mediated, such
11 as reflex sympathetic dystrophy or chronic. Now,
12 those are harder populations to study because it's
13 a rare event, but that certainly is a condition for
14 which we have very few treatment options.

15 Other comments on this question? Dr. Neogi?

16 DR. NEOGI: Just to echo Dr. Rappaport's
17 comment about those that are refractory to standard
18 therapies, I think in osteoarthritis there is some
19 suggestion that there may be central sensitization
20 that accounts for some of the chronic pain, and
21 this might be an opportunity to look at
22 mechanism-driven therapies.

1 DR. BUCKLEY: So if we're done with --

2 DR. LEFF: Sorry. This is Dr. Leff

3 DR. BUCKLEY: Sorry.

4 DR. LEFF: Sorry. I just was trying to
5 follow the conversation to get a sense of the
6 committee. What about types of osteoarthritis? I
7 think I've seen different proposals from the
8 sponsors, either those on waiting lists for joint
9 replacements or those that couldn't get their joint
10 replaced.

11 Is there some discussion about
12 osteoarthritis per se or chronic low back pain,
13 even though there have been studies? Should future
14 studies be possible?

15 DR. BUCKLEY: Comments from the group,
16 committee? Dr. Neogi?

17 DR. NEOGI: I think, at this point, the risk
18 and mitigation strategies we'll be discussing
19 further. But since we don't really know yet that
20 we can be absolutely successful in mitigating this
21 risk, I think we would need to ensure that the
22 people participating in the trials are eligible for

1 surgery. So those that aren't eligible for
2 surgery, if they were to face this devastating
3 outcome, it would be problematic.

4 DR. BUCKLEY: Other comments? Dr. Haque?

5 DR. HAQUE: Yes. I thought we were asking
6 for new issues, rather than whether we were
7 addressing our osteoarthritis.

8 DR. BUCKLEY: Yes. No, you can --

9 DR. HAQUE: Will we be discussing the
10 mitigation factors that industry had put out?

11 DR. BUCKLEY: I think that we're going to
12 proceed to the voting question, and then we'll talk
13 about mitigation strategies.

14 Did you want to speak to mitigation
15 strategies?

16 DR. HAQUE: Well, no. I do think that we
17 should continue trying this in osteoarthritis in
18 the very narrow categories that were brought up by
19 Pfizer and the other representatives.

20 DR. BUCKLEY: So I think there is some
21 consensus from the group that for painful disorders
22 for which we don't have other adequate treatments,

1 unless the patient is particularly at high risk for
2 this event, maybe the committee feels, to
3 understand who in the OA population is most at
4 risk, we still need more information.

5 So we will proceed to the first voting
6 question, question A. I'm going to read the
7 question. If anyone needs clarification of the
8 question, please ask. There's not going to be
9 discussion of the question, but if you just need a
10 clarification of what the question means.

11 There are approved agents that have
12 demonstrated efficacy in reducing pain intensity in
13 conditions such as osteoarthritis. Based on the
14 risk-benefit profile of these agents, is there a
15 role for an ongoing development of the anti-NGF
16 agent?

17 Anyone need clarification of the question
18 from the FDA?

19 [No response.]

20 DR. BUCKLEY: No. Then I think we'll
21 proceed to vote.

22 So to go over the voting procedure, you've

1 noticed that the buttons have started flashing and
2 will continue to flash even after you've entered
3 your vote. You can vote yes, no, or abstain. If
4 you're unsure of your vote, you can change it until
5 the vote is closed. The vote will be displayed on
6 the screen. We'll read the record from the screen.
7 And then we're going to go around the room and ask
8 each of you to state your name, and your vote, and
9 if you want to, why you voted, although you don't
10 need to. And we'll continue to go through the
11 questions in this order.

12 [Vote taken.]

13 DR. BUCKLEY: Okay. Everyone has voted, and
14 the vote is now complete.

15 DR. BAUTISTA: I will now read the vote into
16 the record, 21 yeses, zero nos, zero abstentions.

17 DR. BUCKLEY: Now that the vote is complete,
18 we'll go around the table and everyone who voted,
19 state their name, their vote, and the reason why
20 they voted as they did into the record. And we'll
21 start on this side and move around.

22 DR. BILKER: Warren Bilker. I voted yes.

1 Although there clearly is an increased risk, I feel
2 there is a role for this class of medications.

3 DR. NEATON: Jim Neaton. I voted yes. Kind
4 of following up on that, I guess there is no such
5 thing as a risk-free drug. I think there's a
6 potential niche here. Picking up on something that
7 was said earlier, I think by Dr. Mikuls, I think
8 that there's a lot more work that could be done in
9 potentially identifying people at risk for these
10 conditions. There was a start on it by Dr. Bathon,
11 but she wasn't working with all the data, so
12 hopefully that can be pursued.

13 DR. WALKER: Eric Walker. I voted yes. I
14 do believe there is a role for this agent. I would
15 like to find a way to make it a little bit safer
16 and make sure people who are predisposed to the
17 condition are eliminated.

18 DR. BLOCK: John Block. I voted yes, hoping
19 to see improved pain management in patients.

20 DR. MORRATO: Elaine Morrato. I also voted
21 yes. For me, it was important that the drug data
22 that we saw and the efficacy appears to be more

1 effective than the active control or standard of
2 care. My vote is contingent on the risk
3 minimization steps, which we'll talk about next.

4 The only other thing I would add would be, I
5 think we should be selective in which indications.
6 We've kind of just broadly said such as
7 osteoarthritis. So for example, it wasn't clear to
8 me whether 5-milligram tanezumab is worth pursuing
9 in the chronic low back pain, for example, given
10 the efficacy findings for that indication. So I
11 think it should be indication specific and drug
12 specific based on the available data so far.

13 DR. SUAREZ-ALMAZOR: Maria Suarez-Almazor.
14 I voted yes. I still think the efficacy is modest,
15 but there might be a niche for patients who have
16 severe disease and are refractory to other
17 therapies. And I also feel the safety signals are
18 there, but they appear to be mostly related to the
19 concomitant administration of NSAIDs. And I think
20 there's a need for more data.

21 DR. GABRIEL: Sherine Gabriel. I voted yes.
22 There's clearly a worrisome safety signal. And I

1 agree with Maria that the effect size is likely
2 modest. But in spite of that, I think there's a
3 clinical need here, an unmet need in certain
4 patient populations. And there's also a scientific
5 need to better understand the mechanisms,
6 underlying pain, and develop a new pathway.

7 DR. BLUMENTHAL: This is David Blumenthal.
8 I voted yes, partly because I think this same agent
9 that we're being asked to discuss today probably
10 needs to be scrutinized, knowing what we know now,
11 and not make decisions based on the data as
12 currently available.

13 I think the ideal subjects for a trial of
14 this sort would be patients with osteoarthritis who
15 are at high risk to up with a joint replacement
16 surgery. If I were a back-pain patient and then
17 developed a hip or knee problem or a shoulder
18 problem that required joint replacement surgery, I
19 would be very displeased, I think, with that
20 outcome. I would feel that's not what I signed up
21 for, whereas a patient with advanced osteoarthritis
22 probably understands that that's where they're

1 headed unless this drug can turn things around,
2 then they might be more accepting.

3 DR. BUCKLEY: This is Lenore Buckley. I
4 voted yes for the reasons stated. I think there is
5 significant risk, but there's probably patient
6 populations for which there are not other
7 alternatives, and there may be a role for this
8 drug.

9 DR. MIKULS: Ted Mikuls. I voted yes for
10 all the reasons stated. Also, for me, clearly a
11 well-informed patient will be key, and I'm
12 confident that, that can happen.

13 DR. NEOGI: Tuhina Neogi. I voted yes for
14 the reasons stated previously. I think there is
15 sufficient efficacy data to continue pursuing this,
16 and we need to understand the risk factors for this
17 entity that is leading to these adverse outcomes.

18 DR. LAHITA: Bob Lahita. I voted yes,
19 again, for all the previously stated reasons. I'd
20 like to know more about the pathology. I think
21 nerve growth factors are a very interesting
22 neuroendocrine substance that needs really further

1 study in a big way. And I think the sponsors are
2 in a position to do that.

3 MS. COWAN: Penny Cowan, and I voted yes for
4 many of the same reasons, because we really do need
5 new medications. I think every medication has
6 risks and benefits. I also agree with the
7 information about being an informed consumer, that
8 we really need to have informed consent when these
9 people go into these trials. But I voted yes.

10 MS. BROYLES: Susan Broyles. I voted yes
11 for reasons stated before. I think that we can't
12 close the door to the potential for this class of
13 drugs because it is unique and it has proven or
14 shown that it can be effective.

15 I guess, as far as broad, I think I like the
16 narrower indication initially, particularly for the
17 osteoarthritis patients because of the unsure of
18 the other patients and potential for their joints
19 to experience the same problems. Thank you.

20 DR. BOYCE: I'm Brendan Boyce. I voted yes
21 because I think this looks like a promising new
22 class of drugs. The efficacy seems to be limited

1 to maybe 40 or so percent of patients. And I think
2 it's important that they figure out who these
3 patients are. If the response occurs very early,
4 within a week or two of first injection, it may be
5 that the 60 percent or so of patients who don't
6 respond should not be given further treatment and
7 maybe avoid adverse effects consequently.

8 I think it's also important that the
9 sponsors try and figure out what the mechanism of
10 action of this is to lead to this devastating
11 adverse effect and whether it's with NSAIDs or
12 alone. I would advise that they don't do this in
13 the mouse, which has got an open growth plate,
14 which is different from almost all of the humans
15 who are going to be treated with this, with the
16 exception of kids whose growth plates might be
17 still open. And that would mean probably going to
18 non-human primate subjects. But I think they
19 really should try and figure out what the mechanism
20 is here.

21 DR. KHURANA: I'm Jasvir Khurana. I voted
22 yes for all the reasons said earlier, intractable

1 pain, cancer pain, et cetera. It's less
2 controversial for garden-variety osteoarthritis,
3 perhaps a little bit more difficult. Issues of
4 dosage and medication have been brought up. We use
5 drugs which cause joint necrosis and other things,
6 as Dr. Boyce had pointed out, so putting it all
7 together, there may be a role for it.

8 DR. KELLY: John D. Kelly. I voted yes.
9 This drug, in my estimation, works well. I think
10 it works too well. I think it effectively
11 denervated the joints. I think that the means of
12 delivery has to be tempered. I think that it's an
13 infusion for a cyclical disease. I think if we
14 could solve that problem, I think it will help a
15 lot of people.

16 DR. HAQUE: Mustafa Haque. I also voted yes
17 for many of the above-mentioned reasons. I do
18 appreciate the fact that the FDA did a hold on it
19 because I think it was important to have this
20 review and take a look at all these problems that
21 did occur.

22 But I do appreciate what Dr. Katz was saying

1 about a chilling effect if we don't approve at
2 least some further investigation on this with the
3 development of future drugs. I mean, I don't know
4 if this is going to make final approval eventually,
5 but we do need to look at it further. And my one
6 concern is that patients get a very graphic and
7 informed consent about the potential damage that
8 could occur if they participate.

9 DR. CLEMENS: Tom Clemens. I voted yes for
10 many of the reasons that have been said, especially
11 those by Dr. Boyce.

12 DR. GERSTENFELD: I voted yes. I think that
13 pain management is very important for treating OA,
14 and it's ultimately one of the primary reasons
15 people get their hips replaced. And there really
16 is nothing out there as far as a new class. I
17 think I agreed most with Dr. Blumenthal's
18 assessment that they didn't know what they were
19 getting into. And we didn't have enough adequate
20 data. And the only way to get more is to do
21 better-defined clinical trials with very rigorous
22 informed consent.

1 DR. BUCKLEY: Can I ask you to just state
2 your name into the record?

3 DR. GERSTENFELD: Dr. Gerstenfeld.

4 DR. BOTHWELL: Mark Bothwell. I voted yes.
5 I see a cautious way forward, which will allow the
6 trials to go far enough to see whether this
7 approach has real merit and limiting the risk
8 sufficiently to make it a reasonable proposition.

9 I also think, as others have said, that it's
10 critical to understand the underlying mechanism for
11 these negative outcomes, and I think the sponsors
12 are smart enough and have the resources to attack
13 that problem and make some headway.

14 DR. BUCKLEY: So we will proceed to the next
15 discussion question and then the next voting
16 question. So please discuss whether the anti-NGF
17 agents should be studied only in patients
18 refractory to current standard of care.

19 Anyone who'd like to speak to that issue,
20 please raise your hand.

21 By current standard of care, patients for
22 whom there's no other treatment available -- would

1 that be another way of saying that question,
2 Dr. Rappaport? Should it be limited to patients
3 for which there are no other adequate treatments or
4 have failed other adequate treatments?

5 DR. RAPPAPORT: Who have failed adequate
6 treatments, yes.

7 DR. BUCKLEY: Yes. Right.

8 Dr. Kelly?

9 DR. KELLY: I think since we are talking
10 about different pathways, anything that potentially
11 gets away from the narcotic crisis is worth
12 pursuit. So we shouldn't limit ourselves to those
13 patients who are refractory. We can talk about
14 dosages and milder forms of administration, but
15 absolutely not limit to just those refractory.

16 DR. BUCKLEY: No other comments?

17 [No response.]

18 DR. BUCKLEY: Okay. Then I think we'll
19 proceed to the second voting question. I'll read
20 it and then ask if anyone needs clarification.

21 Is there a role for the ongoing development
22 of anti-NGF agents to manage the pain associated

1 with conditions for which there are no agents with
2 demonstrated analgesic efficacy, such as
3 interstitial cystitis or chronic pancreatitis?

4 Does anyone need clarification of the
5 question?

6 [No response.]

7 DR. BUCKLEY: If not, then we'll proceed to
8 voting. You can see the buttons are flashing; lets
9 you enter your vote.

10 [Vote taken.]

11 DR. BUCKLEY: All the votes have been
12 recorded, and voting will be terminated.

13 DR. BAUTISTA: I will now read the vote into
14 the record, 20 yeses, 1 no, zero abstentions.

15 DR. BUCKLEY: So we will go around the room
16 in the other direction this time. And I'd ask you
17 each to read your name into the record, what your
18 vote was, and if you want to, the reason for your
19 vote.

20 DR. BOTHWELL: Mark Bothwell. I voted yes.
21 I think this is, to me, a simple question. There
22 will undoubtedly always be risks for this approach,

1 but in a select group of diseases, it's certainly
2 justified.

3 DR. GERSTENFELD: This is Dr. Gerstenfeld.
4 I voted yes. I think that, as I said before,
5 there's not a lot of good alternatives currently
6 for pain management, and I think any new compound
7 that makes it to trial should be looked at
8 seriously.

9 DR. CLEMENS: Tom Clemens. I voted yes,
10 with the only caveat that I'm not a physician, so I
11 don't know these other conditions and how
12 problematic they are. But it sounds like this drug
13 could be useful in those conditions.

14 DR. HAQUE: Mustafa Haque. I voted yes
15 because these patients do suffer tremendously and
16 very often don't have other good options.

17 DR. KELLY: John D. Kelly. I voted yes.
18 All pain is neurally mediated, and I see no
19 downside.

20 DR. KHURANA: Jasvir Khurana. I voted yes
21 for all the above reasons.

22 DR. BOYCE: I'm Brendan Boyce. I voted yes.

1 I think there are many conditions where patients
2 have chronic pain. We heard some of the people
3 from the public audience describing some of the
4 pains they have, as well as some of the members of
5 the panel. And finding new agents that can be
6 helpful, at least for a portion of these patients,
7 I think would be a tremendous advance, and that's
8 why I voted yes.

9 MS. BROYLES: Susan Broyles, and I voted yes
10 for the same reason. Anything that has a hope of
11 helping with pain patients, in any way that cycle
12 can be interrupted, is worth pursuing.

13 MS. COWAN: Penny Cowan. And I voted yes
14 because I understand what it's like to live with
15 pain constantly and people that need hope. And
16 this is something that might actually help them
17 long term.

18 DR. LAHITA: Bob Lahita. I voted yes for
19 all of the above reasons.

20 DR. NEOGI: Tuhina Neogi. I voted yes for
21 some of the similarly-state reasons. Here, we have
22 a group of patients who don't have other

1 alternative approved therapies, with the caveat
2 that the same risk mitigation strategies would need
3 to apply.

4 DR. MIKULS: Ted Mikuls. I also voted yes,
5 and I just echo what Dr. Neogi said in terms of
6 risk stratification. Subclinical osteoarthritis is
7 extraordinarily common, and we'll need to keep
8 close tabs on that when we treat these other
9 patient populations.

10 DR. BUCKLEY: Lenore Buckley. I voted yes
11 for the reasons mentioned.

12 DR. BLUMENTHAL: This is David Blumenthal.
13 I guess I'm the lone no vote this time. I guess I
14 see this as a two-stage process, where I would
15 prefer to get better data on how much of a problem
16 the bone and joint disease is really going to be,
17 and whether the risk mitigation strategies that the
18 sponsor has suggested are actually going to work,
19 before I have people who do not yet need a joint
20 replacement take the risk of possibly getting a
21 joint replacement.

22 So I would have wanted to see phase 1 before

1 moving on to this, which would be phase 2.

2 DR. GABRIEL: Sherine Gabriel. I voted yes.
3 For me, the most important phrase is "conditions
4 for which there are no agents with demonstrated
5 analgesic efficacy."

6 DR. SUAREZ-ALMAZOR: Maria Suarez-Almazor.
7 I voted yes, nothing else to add.

8 DR. MORRATO: Elaine Morrato. I also voted
9 yes for the reasons stated by others.

10 DR. BLOCK: John Block. I voted yes. I
11 believe that there may be a path which would
12 mitigate the risk in patients who have relatively
13 normal joints, and I'd like to see it pursued in
14 patients who have no other options.

15 DR. WALKER: Eric Walker. I voted yes. As
16 long as the patient is aware of the small
17 possibility of a joint complication, they certainly
18 can decide if they're willing to take the risk for
19 maybe increased quality of life and loss of their
20 chronic pain.

21 DR. NEATON: Jim Neaton. I voted yes for
22 the reasons that have been stated.

1 DR. BILKER: Warren Bilker. I voted yes
2 along the lines of what Dr. Walker just said. I
3 think it's imperative that the risks, although
4 there is an increased risk, be very clearly and
5 strongly stated in the consent form.

6 DR. BUCKLEY: We are going to proceed to the
7 next discussion point, J. In I, we talked about
8 whether the use should be limited -- or studied
9 only in patients refractory to current
10 therapy -- or patients refractory to current
11 therapy, and that referred to OA patients.

12 Now, we're going to ask the same question
13 and discuss whether in the group for whom we just
14 took the vote, patients with conditions for which
15 there are no agents with demonstrated efficacy such
16 as interstitial cystitis or carrying chronic
17 pancreatitis, should the use in this
18 population -- we've already talked about the OA
19 population, but now, this population -- should that
20 be studied only in patients who are refractory to
21 other treatments or would there be other groups for
22 which this anti-NGF treatment would be appropriate?

1 Any comments? Yes, Dr. Gabriel?

2 DR. GABRIEL: Just a point of clarification.
3 So I'm a bit confused. We just voted based on the
4 condition that there are no agents with
5 demonstrated analgesic efficacy. And now we're
6 asking only in patients, whoever, refractory. It
7 seems like it's the same thing.

8 DR. BUCKLEY: Dr. Rappaport, do you want to
9 clarify how you'd like us to approach this?

10 DR. RAPPAPORT: I think that was a very
11 astute observation.

12 [Laughter.]

13 DR. RAPPAPORT: I think you can move on.

14 DR. BUCKLEY: So now we move on to the I
15 think even more challenging question. so we'll
16 proceed to 4.

17 If clinical trials are allowed to proceed,
18 discussion point A, what screening procedures,
19 safety monitoring, and follow-up assessments should
20 be included in the studies?

21 Dr. Walker?

22 DR. WALKER: Yes. I agree with the

1 sponsors' decision to obtain a baseline radiograph
2 on all the large joints. And they might want to
3 also consider a baseline MRI of the pelvis, because
4 although it's expensive, it would be much more
5 sensitive for pre-existing conditions, subchondral
6 fracture, AVN, marrow edema, or synovitis. That's
7 all.

8 DR. BUCKLEY: Dr. Neaton?

9 DR. NEATON: I was going to say that I also
10 agree with the proposal to follow everybody six
11 months after the end of the study. And I take that
12 to be along the lines that Dr. Braunstein mentioned
13 a while back, that everybody, no matter when they
14 stopped treatment, at the end of the study would be
15 another six months.

16 I also would support a longer-term study
17 than what we saw here today, closer to the two
18 years that I gather Regeneron was planning to do
19 that got cut short, given the lifelong use of many
20 of these treatments.

21 For the data monitoring committee, given the
22 rarities of these events, I think it's really

1 important that the monitoring guidelines be very
2 clearly articulated before you begin the study for
3 these types of events and consider -- because I
4 don't see any evidence at this point that this is
5 not a class effect; we just have less data from two
6 sponsors -- to consider some type of a
7 collaboration where the information is combined.

8 DR. BUCKLEY: Thank you.

9 Dr. Neogi?

10 DR. NEOGI: I agree that MRI should be used
11 for screening and follow-up in addition to the
12 x-ray. I think the x-ray findings will be later in
13 the course of whatever this process is. And
14 screening with MRI at baseline would be important
15 not only for the index joint, but for other at-risk
16 joints that have been picked up in the data so far.

17 Frequency, I also agree, should be sooner
18 than once a year, particularly since some of the
19 examples we were given were changes that occurred
20 by eight months or so. And that just happened to
21 be because of the timing of the symptoms and
22 assessment.

1 In terms of long-term follow-up, if I recall
2 correctly, I think it was stated that for those
3 that have a joint replacement, follow-up would be
4 extended for three months after that joint
5 replacement. So I think that's too short a time
6 for evaluation of these types of bone pathologies.

7 I also think that given the degree of bone
8 changes that we're seeing, further assessments of
9 bone, whether it be biomarkers, others,
10 bone-specific imaging, or DEXA, other osteoporosis
11 marker, something to give us a better sense of
12 what's going on with the bone for these
13 individuals, in addition to the neuropathy
14 screening that is already in place.

15 DR. BUCKLEY: Dr. Block?

16 DR. BLOCK: This is John Block. The
17 committee commented that from I, on the first page,
18 the increased load theory, which would incriminate
19 articulate cartilage as the thing that gets damaged
20 first is not particularly attractive as an idea.
21 And, therefore, I think a lot of focus needs to be
22 spent on the subchondral bone as the site of

1 interest.

2 With that having been said, I don't think
3 that measurement of articular space is particularly
4 useful for early detection. I think there needs to
5 be a focus on radiographic and MRI evaluation of
6 the subchondral bone.

7 Also with that in mind, I think that bone
8 mineral density evaluation as it might relate to
9 the propensity to develop subchondral insufficiency
10 fracture and then incongruent joint surfaces, I
11 think would be helpful.

12 DR. BUCKLEY: Dr. Boyce?

13 DR. BOYCE: Brendan Boyce. I, too, think
14 that pathology of any hip replacement or knee
15 replacement specimens should be reviewed. The
16 sections should be taken in a uniform fashion, and
17 the histologic sections should be studied by an
18 expert, and not just rely upon the report from some
19 local pathologist, because a pathologist's ability
20 to diagnose osteonecrosis is limited. There's not
21 a lot of specific training in that.

22 I know when I meet with radiologists and

1 review cases where there is osteonecrosis, the
2 radiologists often don't agree with the pathology
3 or among one another. And again, I think these MRI
4 images, if it's going to be MRI and radiographs,
5 should be reviewed by experts in interpreting
6 these.

7 I think it's also likely that looking at
8 bone markers would be worthwhile as well,
9 particularly if it is, as we see in mice, an
10 increase and a marker of bone resorption.

11 What you wouldn't want to do is have
12 increased osteoclast activity associated with a
13 systemic increase in bone resorption and an
14 associated risk of developing osteoporotic
15 fractures such as compression fractures or
16 fractures elsewhere that would be associated with
17 the trauma that post-menopausal women and
18 osteoporotic men can suffer.

19 DR. BUCKLEY: Thank you.

20 Dr. Kelly?

21 DR. KELLY: At the expense of being a little
22 curt, I think you should scrap the whole total

1 joint index and just follow patients longitudinally
2 with WOMAC scores and longitudinal x-rays. I think
3 there'd be some measure of kinesthetic sense and
4 proprioception. Even though they said protective
5 sensation was preserved, it doesn't indicate
6 kinesthesia or proprioception.

7 The third thing I would do is, I would
8 exclude diabetics. I think there may be some
9 underlying double crush here at work, where people
10 with underlying, low-graded neuropathy may be more
11 susceptible to these agents.

12 DR. BUCKLEY: Dr. Kelly?

13 I'm sorry. Dr. Morrato?

14 DR. MORRATO: Yes. Elaine Morrato. I
15 wanted to expand a little bit our thinking in terms
16 of safety monitoring and in thinking about the end
17 goal of how the data will translate from the trials
18 into clinical practice in what might be proposed
19 risk management plans at the time the drug is up
20 for approval or launch.

21 I think we can all agree that risk
22 minimization measures need to be practical and

1 realistic -- fit with normal routines of clinical
2 care. And I think the challenge will be in doing
3 the trials, balancing the rigor that we want to
4 collect in the trials in order to answer these
5 questions, with also making the goals of risk
6 management practical for the patients and
7 clinicians involved.

8 So I've seen many programs in which you
9 build in a lot of rigor in the trials, and then
10 that becomes your risk management program when it
11 commercializes, and it becomes untenable.

12 So I have a few suggestions based on what
13 the sponsors had proposed. So, for instance,
14 patient-informed consent, so I would agree that's
15 very important, as Ms. Cowan and others have
16 mentioned. But how do we do that in a way that can
17 be translatable when it actually goes to market?
18 Because they're not necessarily going to be filling
19 out a multi-page thing that you do in the trial.

20 So related to that would be excluding
21 chronic concomitant NSAID use, so a study could
22 look into comprehension and intended behaviors that

1 would be related to the patient or physician-
2 directed education materials. I think these kinds
3 of studies could run in parallel with the clinical
4 trials, such that you have more comprehensive
5 information at the end.

6 The same thing is with how are you going to
7 practically exclude patients with pre-existing
8 rapidly progressive OA from treatment in clinical
9 practice. Will you be asking all joints to be
10 x-rayed before drug is started? So thinking
11 through of what the end goal is, such that the data
12 collection analysis is supporting that.

13 The same thing as I brought up in questions
14 earlier around, discontinuing patients who did not
15 respond adequately to initial doses, starting to
16 conceptualize how that might be described so that
17 that's built into the clinical programs so you're
18 collecting that data, and that also is dependent
19 upon how the drug is being dosed.

20 Same thing in terms of looking at the NSAID
21 use over time; how will reminders be managed with
22 the patient when the drug is being dosed on longer

1 intervals than some between assessments?

2 So you have much more frequent trial visits
3 than you might have in clinical practice. And I
4 think the measures you're collecting around safety
5 and knowledge needs to match up with how it
6 ultimately will be used.

7 I just think making sure you think of
8 careful thought of how this information will be
9 operationalized assuming you get good risk
10 minimization results, and collecting the patient
11 and physician -- sort of market or consumer
12 understanding research, so that can supplement the
13 application at the end.

14 DR. BUCKLEY: Thank you.

15 Dr. Lahita?

16 DR. LAHITA: Yes. Lahita. I want to -- and
17 I don't know if this is already being done, that
18 the MRIs and all radiologic films be read at a
19 central location by two or more radiologists and
20 also available for analysis if this committee is
21 reconvened, so that we can safely say that the FDA
22 and others have access to the films, the original

1 films.

2 Secondly, I also would prohibit use of
3 NSAIDs in any future studies.

4 DR. BUCKLEY: Dr. Gerstenfeld?

5 DR. GERSTENFELD: I just had one additional
6 caveat in terms of consideration of subchondral
7 bone, whether that be a consideration of acute
8 corticosteroid administration or longitudinal
9 corticosteroid administration, since that's
10 associated with bone loss as well.

11 DR. BUCKLEY: No other comments? Yes?

12 DR. KHURANA: Yes. Jasvir Khurana. Some
13 suggestions for follow-up and study. Radiology I
14 think has been mentioned, including unusual areas
15 like the ankle. There are several serum markers
16 for the question-mark fractures, pyridinoline,
17 hydroxyproline, urinary studies of that, bone
18 formation alkaline phosphatase, acid phosphatase.

19 The pathology should be done at a
20 centralized location, as Dr. Boyce mentioned.
21 There's a lot of variation between pathologists,
22 the interpretation and so forth. It has to be done

1 by someone who's actually interested in doing this.
2 And it should be done by protocol.

3 Several organs are done that way. Patients
4 with BRCA1 or BRCA2 mutations get the entire ovary
5 and fallopian tube sampled according to a specific
6 protocol. Something similar to that should be done
7 for hips or bone removed from joints for this and
8 be studied at a central point.

9 DR. BUCKLEY: Thank you.

10 So to summarize, there's been a wealth of
11 ideas, and I'm not going to get all of them. But
12 to summarize, I think people feel, for screening,
13 that there need to be extensive baseline
14 radiographs, especially of target joints like hip
15 and knees, shoulders, and that these need to be
16 followed fairly closely through the trial. And, in
17 fact, after the end of the trial, they need to be
18 followed for a long period of time.

19 MRI was also suggested for baseline
20 screening and for follow-up to get a better idea of
21 what's going on. And we'd look at both bone
22 cartilage and the issue of tendon and possible

1 tendon rupture.

2 I think this group is concerned about other
3 metabolic effects of these agents and feels that
4 bone needs to be carefully looked at. A suggestion
5 such as looking at bone biochemically, looking at
6 DEXA and trying to find out what's going on within
7 bone.

8 The issue of falls, falls as relating to
9 fractures, but with a drug that might have some
10 neurologic effects and with falls relating to
11 fractures to maybe, as in osteoporosis study, keep
12 count of falls that are occurring.

13 We've talked about continuing neurologic
14 studies, kinesthetics, and proprioception through
15 the trial, maybe into long-term studies and in a
16 population of patients that are coming off as well,
17 that those might be important things to do.

18 The issue of long-term follow-up has been
19 repeated again and again, the importance of a
20 central lab to look at pathology, histology,
21 radiology, so that we have some consensus. The
22 importance of excluding certain populations in the

1 screening procedures, especially diabetics, has
2 been brought up.

3 I think with that summary, any other
4 questions that we need to address on that point,
5 Dr. Rappaport?

6 No. Okay.

7 So now we get to NSAID use. And I'm going
8 to try to combine these two points. I don't know
9 if they're the same on your screen as mine.

10 Do the data support allowing clinical trials
11 to proceed with some amount of concurrent NSAID
12 use? And if clinical trial studies limit
13 concurrent NSAID use, can NSAID use be limited
14 post-approval?

15 I'll open that just for discussion.

16 Dr. Clemens, to start?

17 DR. CLEMENS: I mean, I would be worried
18 about that. Let me just make a point. There's a
19 lot known about the basic mechanisms, whereby COX,
20 and cyclooxygenase inhibitors, and this family of
21 drugs inhibits angiogenesis, either directly or
22 through blocking inflammatory mediators that are

1 known to be involved in the initial angiogenic
2 response to healing.

3 So I think I'd be very skeptical about the
4 continued use of those two drugs in combination.

5 DR. BUCKLEY: Dr. Kelly?

6 DR. KELLY: I would echo those sentiments
7 and also add that we've got to pick our battles
8 here. This is one pathway we should focus on, and
9 we do know the rheumatology and the matrix effects
10 of NSAIDs, the proteoglycan depletion, and some of
11 the longitudinal studies showing joint wear. So I
12 do think we ought to just lay low on that one.

13 DR. BUCKLEY: Yes. Dr. Haque?

14 DR. HAQUE: I agree with Dr. Kelly and
15 Dr. Clemens. And I think that you can limit this
16 afterwards. I mean, you can treat it as just a
17 straight contraindication, the way we do with other
18 medications. People on Plavix don't take NSAIDs.
19 If a patient wants to continue on this medication,
20 then that's out of the question.

21 DR. BUCKLEY: Other comments? Does anyone
22 want to comment on whether we're going to be able

1 to limit NSAID use post-approval, whether that's
2 practical out in practice?

3 Dr. Mikuls?

4 DR. MIKULS: I just want to make one comment
5 that'll be important to think about going forward,
6 and that'll be just the low-dose NSAID use,
7 prophylactic aspirin use, which is almost universal
8 in some ways for cardiac prevention. And what
9 doses we're talking about, what defines an NSAID
10 dose is going to be important to think about.

11 You may want to study those patients because
12 you may want to know the answer to that question.

13 DR. BUCKLEY: So I think in summary, there's
14 general concern about studies moving forward
15 including NSAID use, really, on any basis, either
16 intermittent or chronic. But there are I think
17 concerns in the committee about the ability to
18 control NSAID use in the community. And the issue
19 I think that's been brought up a number of times by
20 Dr. Morrato, which is REMS and how you educate, I
21 mean, we educate patients on Coumadin not to take
22 NSAIDs, sometimes successfully, sometimes less

1 successfully. But there would clearly need to be a
2 program in place to make patients aware of this
3 risk.

4 Any other comments on this question?

5 [No response.]

6 DR. BUCKLEY: We're moving through. We're
7 making progress.

8 Discussion on point 5. Are there additional
9 non-clinical studies that can be conducted that may
10 provide additional insight into the possible
11 etiologies for bone and joint adverse events noted
12 during the clinical development of the anti-NGF
13 agents?

14 Dr. Haque? I'm sorry. Dr. Block?

15 DR. BLOCK: With regard to the joint
16 destruction, one of the mechanisms that was
17 considered was whether or not this was a
18 neuropathic arthropathy. And I think that's a very
19 useful line to pursue. Every time we try to blame
20 something on osteonecrosis, we get humbled. I
21 think spontaneous osteonecrosis of the knee is an
22 example of that, which is probably not spontaneous

1 osteonecrosis. And I think Freiberg's infraction
2 is another consideration, which is probably not
3 osteonecrosis.

4 So with the consideration that this may be
5 neuroarthropathic, a lot of attention was spent on
6 the neurotraumatic pathways. And we've had a bunch
7 of sponsors who were very geared up to present
8 information about proprioception and other causes
9 of neuropathy or other results of neuropathy.

10 But vascular dysregulation is another
11 pathway. And why we focus a lot on
12 osteonecrosis -- and you can find osteonecrosis
13 wherever you look. You can find it in
14 osteoarthritis. We know that. And you can find it
15 in a lot of other things -- vascular dysregulation
16 also can lead to neuropathic joints.

17 Now, the only thing I saw about vascular
18 dysregulation was in the RGN475 research, which
19 looked at vascular density, but vascular density is
20 different than hyperemia.

21 So I would suggest -- and I don't know how
22 to do this. I'm going to be honest with you. I

1 would suggest that looking for hyperemia around the
2 joints, which can be very destructive to
3 subchondral bone and can lead to subchondral
4 collapse, and can lead to neuropathic-like joints,
5 would be a very useful non-clinical study to
6 perform.

7 DR. BUCKLEY: Dr. Bothwell?

8 DR. BOTHWELL: Yes. I think this question
9 can be so divided into a couple of questions. The
10 first question that has to be addressed is which
11 cells are responding to NGF that causes this effect
12 when you remove it.

13 So there are two possibilities. It's either
14 the sensory neurons, their axons, or it's a non-
15 neural cell, and there certainly are examples of
16 TrkA and P75 receptors being expressed on non-
17 neural cells, although I'm not aware of any of them
18 being in joint.

19 That can be approached very easily because
20 the sensory axons, the cell bodies, are far away
21 from the joint. So if there's RNA for P75 or TrkA
22 in the joint, then a non-neural cell is a likely

1 candidate that needs to be considered and needs to
2 be identified.

3 So I think that's the place to start, is
4 figuring out which cells have the targeted
5 receptors.

6 DR. BUCKLEY: No other discussion points.

7 So I think that the suggestions from the
8 group about additional non-clinical studies that
9 might provide additional insight are looking at
10 vascular effects of these agents and especially
11 vascular effects in bone; looking at the neurologic
12 effects and neurotoxic effects; looking at bone
13 markers and biomarkers, some data of which was
14 presented today; and looking to see if the
15 receptors on other tissues might be responsive, or
16 where there might be toxic effects; and finally,
17 continuing to look at the issue of fractures and
18 the type of fractures that are seen on histology.

19 Any other comments?

20 [No response.]

21 DR. BUCKLEY: Dr. Rappaport, do you have any
22 other questions you would like us to address? No.

1 Dr. Kelly?

2 DR. RAPPAPORT: No. Thank you very much.

3 We appreciate your input.

4 DR. KELLY: I just want to follow up on what
5 Dr. Block said. I think that a triple phase
6 bones -- looking at soft tissue uptake would answer
7 the hyperemia question.

8 DR. BUCKLEY: Dr. Rappaport, did you want to
9 make any concluding remarks to the committee?

10 DR. RAPPAPORT: No. As I said, thank you.
11 It's been very useful discussion, and we appreciate
12 your time.

13 **Adjournment**

14 DR. BUCKLEY: So I want to thank everyone
15 today. There's been a tremendous amount of work
16 and information that's been brought to us, and
17 that's been reviewed, and a great discussion. I
18 appreciate everyone's work, and I hope you all have
19 a good and restful evening.

20 We'll now adjourn the meeting. Please
21 remember to drop off your name badge at the
22 registration table on your way out, so that it can

1 be recycled. Thank you.

2 (Whereupon, at 4:29 p.m., the meeting was
3 adjourned.)

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