

1 FOOD AND DRUG ADMINISTRATION
2 CENTER FOR DRUG EVALUATION AND RESEARCH

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4
5 MEETING OF THE
6 ARTHRITIS ADVISORY COMMITTEE (AAC)

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10 Tuesday, June 21, 2011

11 8:30 a.m. to 3:45 p.m.
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19 The Marriott Inn & Conference Center

20 3501 University Boulevard East

21 Hyattsville, Maryland
22

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

2 (8:29 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

5 DR. O'NEIL: Good morning, everyone. First
6 let me remind everyone to please silence your cell
7 phones and other electronic devices if you have not
8 already done so.

9 I would like to identify the FDA press
10 contact, Ms. Morgan Liscinsky.

11 Could you please stand? Thank you.

12 My name is Kathleen O'Neil, and I am a
13 pediatric rheumatologist from the University of
14 Oklahoma. I will serve as chair of this meeting.
15 And I'd like to ask the panelists to identify
16 themselves, beginning with Dr. Fletcher.

17 DR. FLETCHER: Good morning. I'm Mark
18 Fletcher. I am the nonvoting industry
19 representative on the Arthritis Advisory Committee.
20 Background is in allergy, immunology, rheumatology.
21 More than 17 years in the industry, most recently
22 Pfizer. But I'm an independent consultant at the

1 present time.

2 DR. PEDUZZI: I'm Peter Peduzzi, temporary
3 member of the committee. I'm director of the Yale
4 Center for Analytical Sciences. My background is
5 biostatistics and clinical trials.

6 DR. FELSON: My name is David Felson. I'm a
7 temporary member of the committee. I'm a
8 rheumatologist and epidemiologist from Boston.

9 DR. NEOGI: Tuhina Neogi, also temporary
10 voting member, rheumatologist and epidemiologist
11 from Boston.

12 DR. GIBOFSKY: Allan Gibofsky, temporary
13 member of the committee, rheumatologist and public
14 health, New York, Cornell.

15 MR. SNARSKY: Richard Snarsky. I'm the
16 patient representative. I have gout, and I also
17 have arthritis, and feel that I can offer my
18 50 cents worth. Thank you.

19 MS. ARONSON: Diane Aronson. I'm from
20 Cambridge, Massachusetts, and I'm serving as the
21 consumer representative.

22 DR. SUAREZ-ALMAZOR: Maria Suarez-Almazor,

1 University of Texas in Houston. I'm a
2 rheumatologist with expertise in clinical
3 epidemiology.

4 DR. BUCKLEY: I'm Lenore Buckley. I'm an
5 adult and pediatric rheumatologist at Virginia
6 Commonwealth University in Richmond, Virginia.

7 DR. BAUTISTA: My name is Philip Bautista.
8 I'm the designated federal officer for the
9 Arthritis Advisory Committee.

10 DR. MIKULS: Ted Mikuls, a rheumatologist/
11 epidemiology at the University of Nebraska.

12 DR. BLUMENTHAL: David Blumenthal, a
13 rheumatologist at the VA Medical Center and Case
14 Western Reserve University in Cleveland.

15 DR. KERR: Gail Kerr. I'm a rheumatologist
16 at the VA Medical Center in Washington, D.C.

17 DR. DAVI: Ruthanna Davi. I'm the
18 statistical reviewer for this application at the
19 FDA.

20 DR. LAPTEVA: Larissa Lapteva. I'm a
21 clinical reviewer for this application from the
22 Division of Pulmonary, Allergy, and Rheumatology

1 Products.

2 DR. OKADA-YIM: Hi. My name is Sarah Okada-
3 Yim. I'm clinical team leader for rheumatology and
4 adult rheumatologist.

5 DR. CHOWDHURY: I'm Badrul Chowdhury. I'm
6 the division director in the Division of Pulmonary,
7 Allergy, and Rheumatology Products.

8 DR. ROSEBRAUGH: Curt Rosebraugh, director,
9 Office of Drug Evaluation II.

10 DR. O'NEIL: Thank you.

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

21 In the spirit of the Federal Advisory
22 Committee Act and the Government in the Sunshine

1 Act, we ask that the advisory committee members
2 take care that their conversations about the topic
3 at hand take place in the open forum of the
4 meeting.

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

12 Now I'll pass it to Phil, who will read the
13 conflict of interest statement.

14 **Conflict of Interest Statement**

15 DR. BAUTISTA: Thank you. The Food and Drug
16 Administration is convening today's meeting of the
17 Arthritis Advisory Committee under the authority of
18 the Federal Advisory Committee Act of 1972. With
19 the exception of the industry representative, all
20 members and temporary voting members of the
21 committee are special government employees or
22 regular federal employees from other agencies, and

1 are subject to federal conflict of interest laws
2 and regulations.

3 The following information on the status of
4 this committee's compliance with federal ethics and
5 conflict of interest laws covered by, but not
6 limited to, those found at 18 USC Section 208 and
7 Section 712 of the Federal Food, Drug and Cosmetic
8 Act, is being provided to participants in today's
9 meeting and to the public.

10 FDA has determined that the members and
11 temporary voting members of the committee are in
12 compliance with federal ethics and conflict of
13 interest laws. Under 18 USC Section 208, Congress
14 has authorized FDA to grant waivers to special
15 government employees and regular federal employees
16 who have potential financial conflicts when it is
17 determined that the agency's need for a particular
18 individual's services outweighs his or her
19 potential financial conflict of interest.

20 Under Section 712 of the FD&C Act, Congress
21 has authorized FDA to grant waivers to special
22 government employees and to regular federal

1 employees with potential financial conflicts when
2 necessary to afford the committee essential
3 expertise.

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

15 Today the committee will discuss the
16 supplemental biologic license application 125319
17 for Ilaris, canakinumab, by Novartis
18 Pharmaceuticals for the "treatment of gouty
19 arthritis attacks in patients who cannot obtain
20 adequate response with NSAIDs or colchicine.
21 Ilaris has also been shown to extend the time to
22 next attack and reduce the frequency of subsequent

1 attacks."

2 Based on the agenda for today's meeting and
3 all financial interests reported by committee
4 members and temporary voting members, no conflict
5 of interest waivers have been issued in connection
6 with this meeting.

7 To ensure transparency, we encourage all
8 standing committee members and temporary voting
9 members to disclose any public statements that they
10 have made concerning the product at issue.

11 With respect to FDA's invited industry
12 representative, we would like to disclose that
13 Dr. Mark Fletcher is participating in this meeting
14 as a nonvoting industry representative, acting on
15 behalf of regulated industry. Dr. Fletcher's role
16 at this meeting is to represent industry in general
17 and not any particular company. Dr. Fletcher is
18 self-employed.

19 We would like to remind members and
20 temporary voting members that if the discussion
21 involves any other products or firms not already on
22 the agenda for which an FDA participant has a

1 personal or imputed financial interest, the
2 participants need to exclude themselves from such
3 involvement, and their exclusion will be noted for
4 the record.

5 FDA encourages all other participants to
6 advise the committee of any financial relationships
7 that they may have with any firms at issue. Thank
8 you.

9 DR. O'NEIL: Thank you.

10 Next I would like to introduce Dr. Badrul
11 Chowdhury, the director of the Division of
12 Pulmonary, Allergy, and Rheumatology Products at
13 CDER at the FDA.

14 DR. CHOWDHURY: Thank you, Dr. O'Neil. And
15 on behalf of the FDA, I welcome members of the
16 advisory committee, members of Novartis and their
17 consultants, and all in the room and elsewhere to
18 the meeting. We appreciate you chairing the
19 meeting and being here and advising us on this
20 important matter.

21 I turn it over to Dr. Sarah Okada-Yim to
22 give the introductory remarks for the agency.

1 Thank you.

2 **Opening Remarks**

3 DR. OKADA-YIM: Okay. Thank you. Good
4 morning. I'm going to give you just a very brief
5 overview of the issues for discussion for today.

6 Canakinumab is a recombinant human
7 monoclonal antibody targeting interleukin-1 beta.
8 This molecule has a prolonged half-life and
9 pharmacodynamic effects, with a terminal half-life
10 of up to 26 days.

11 The original BLA was approved June 17, 2009
12 for use as a treatment for the rare genetic
13 disorder of cryopyrin-associated periodic
14 syndromes, where the dosing interval is every two
15 months. The proposed gout indication would greatly
16 expand the potential population of canakinumab
17 users.

18 The canakinumab clinical program for gout
19 consisted of two identical pivotal studies of 12
20 weeks duration, with a 12-week blinded extension
21 followed by a one-year open label extension. Prior
22 to the pivotal studies, two dose-ranging studies

1 were performed, one single-dose acute gout
2 treatment dose-ranging study, H2255, of 8 weeks
3 duration, and one chronic gout treatment dose-
4 ranging study of 24 weeks duration, with a 24-week
5 open label extension. In the chronic gout
6 prophylactic treatment study, only one arm had
7 multiple dosing.

8 The initial proof of concept study only
9 contained 3 patients with 10 milligrams per
10 kilogram of IV canakinumab, and 3 patients treated
11 with 12 milligrams of dexamethasone IV as a
12 comparator.

13 The indication being sought is "treatment of
14 gouty arthritis attacks in patients who cannot
15 obtain adequate response with NSAIDs or colchicine.
16 Ilaris has also been shown to extend the time to
17 next attack and reduce the frequency of subsequent
18 attacks." The proposed dose and administration is
19 150 milligrams subcutaneously as a single dose.

20 Canakinumab was better than triamcinolone
21 for the primary endpoints of change in pain
22 intensity at 72 hours and time to first new flare,

1 and the differences were statistically significant.
2 The endpoint of pain at 72 hours is more reflective
3 of acute treatment, and the endpoint of time to
4 first new flare is more reflective of the extended
5 pharmacodynamic effects of the molecule. Although
6 relevant and important in the setting of acute gout
7 flares, these endpoints would not be considered
8 disease-modifying but rather symptomatic benefits.

9 As will be discussed in further detail,
10 canakinumab treatment was associated with
11 undesirable effects that were notable after a
12 single 150-milligram dose. These include
13 infections, neutropenia, hypertriglyceridemia, uric
14 acid elevation, decreased creatinine clearance, and
15 hypertension adverse events. Effects on laboratory
16 parameters were protracted and also noted on
17 retreatment.

18 In light of the primarily symptomatic
19 benefits versus the safety concerns identified, the
20 fact that only one dose of canakinumab was studied
21 in retrospect leaves one wanting for more. In the
22 dose-ranging study in acute gout, the 150-milligram

1 dose was statistically superior to triamcinolone.
2 However, superiority to triamcinolone was not an
3 agency requirement.

4 Results for 10 milligrams through
5 90 milligrams suggest these doses could also have
6 been efficacious. The point estimates were
7 numerically slightly better than triamcinolone, and
8 cumulative flare rates for 10 milligrams and
9 50 milligrams were equivalent to the 150-milligram
10 dose. It is possible that one of these doses could
11 have had a more favorable risk/benefit profile.

12 As a reminder of the purpose of these
13 proceedings, FDA will be asking the committee for
14 their advice and recommendations on these matters,
15 although FDA retains discretion regarding actions
16 to be taken or policy to be expressed.

17 As you listen to the presentations that
18 follow, we ask that you keep risk/benefit
19 considerations in mind. These considerations
20 include, canakinumab's extended effects after a
21 single injection, with limited safety data
22 available on recurrent or chronic use; the non-

1 disease-modifying nature of the benefit versus
2 increased risks of serious infection and
3 undesirable laboratory abnormalities after a single
4 injection; the fact that the patient population for
5 whom treatment would be indicated may not be
6 considered refractory; and, finally, the fact that
7 data are mostly available for the 150-milligram
8 dose, and it's not known whether a lower dose would
9 have had a better risk/benefit profile.

10 With that, I'll turn it over back to you,
11 Dr. O'Neil. Thank you.

12 DR. O'NEIL: Thank you, Dr. Okada-Yim.

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

20 For this reason, FDA encourages all
21 participants, including the sponsor's non-employee
22 presenters, to advise the committee of any

1 financial relationships they may have with the firm
2 at issue, such as consulting fees, travel expenses,
3 honoraria, and interests in the sponsor, including
4 equity interests and those based upon the outcome
5 of the meeting.

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

13 We will now proceed with the sponsor's
14 presentations. The first speaker from Novartis
15 Pharmaceuticals Corporation is Dr. Trevor Mundel,
16 global head of development at Novartis Pharma AG.
17 Dr. Mundel.

18 **Sponsor Presentation - Trevor Mundel**

19 DR. MUNDEL: Dr. O'Neil, members of the
20 Advisory Committee, FDA, I'm Trevor Mundel. I head
21 up the development group at Novartis. And I want
22 to thank you on behalf of the canakinumab team, the

1 gout patients, and the gout physicians who
2 participated in our program for this opportunity to
3 discuss our program with you today.

4 Canakinumab is a novel and potent selective
5 anti-inflammatory which interrupts IL-1 signaling
6 by neutralizing specifically IL-1 beta. It's
7 interesting that, if approved, it would be the
8 first new therapy in almost half a century to treat
9 the acute inflammation in gout, one of the oldest
10 recognized medical conditions.

11 A single injection of canakinumab has got
12 two benefits. Firstly, it treats the acute
13 inflammation of the gout attack; and secondly, it
14 suppresses subsequent attacks in a majority of
15 patients, as we've seen in our phase 3 program,
16 potentially for over 6 months.

17 We've thought long and hard about where this
18 therapy would best be directed, and we came to the
19 conclusion that it would be best reserved for the
20 most severe gout patients, the 6 percent of
21 diagnosed gout patients who really cannot get
22 adequate relief from the standard medications,

1 nonsteroidals, or colchicine. These are patients
2 who are also having a lot of attacks. We required
3 more than three attacks in our clinical program,
4 but these patients reported over six attacks every
5 year.

6 I know that many of you are familiar with
7 what a gout attack entails, but for those of you
8 who are not, I did want to put up the classic
9 description by a physician more than 300 years ago,
10 Thomas Sydenham. He was also a gout sufferer. And
11 he said that it was waking up in the middle of the
12 night with a pain that was like a dislocation of
13 your joint, so intense that he could not tolerate
14 the bedclothes over his inflamed joint, and he
15 could not even tolerate the jarring of somebody
16 walking in the same room.

17 These are complex patients. These are not
18 patients who are easily treated with a prescription
19 of, take your uric acid-lowering therapy, change
20 your diet, and do more exercise. Many of these
21 patients, complex patients, have difficulty
22 controlling their attacks.

1 Canakinumab neutralizes IL-1 beta, and it's
2 important to recognize that this is very selective.
3 Of the ligands that act at the IL-1 receptor, it
4 does not interfere with IL-1 alpha or the IL-1
5 receptor antagonist.

6 The new science that has so excited the
7 field of gout, and what we are trying to take
8 advantage of now, is that unlike the nonselective
9 agents for inflammation, the nonsteroidals,
10 glucocorticoids, colchicine, canakinumab actually
11 interrupts directly the pathogenic pathway of
12 inflammation in gout.

13 How this works is that uric acid crystals,
14 which are highly irritant, trigger a pattern
15 recognizer inside cells, particularly macrophages,
16 which is called the inflammasome. And this
17 inflammasome then splits the precursor of IL-1 beta
18 into the active IL-1 beta, which triggers the
19 inflammation cascade in gout. And that is what
20 canakinumab specifically is interrupting.

21 We have an extensive program, and in that
22 program we have followed the philosophy of, follow

1 the science. Go where this would specifically be
2 used. For that reason, we first directed this to
3 the rare autoinflammatory disorder CAPS, for which
4 we have a registration. We have now 300 patients,
5 at least, who have been treated for up to five
6 years with good safety and great benefit in that
7 indication.

8 Under review today is the gouty arthritis
9 indication. We have a supportive program in
10 rheumatoid arthritis, which is I think very
11 significant to the proceedings today because there
12 we have higher doses of canakinumab, up to
13 300 milligrams, where patients were dosed every
14 2 weeks out to over 18 months. And the safety over
15 there would seem to be not different from placebo.

16 We also have a phase 3 program in systemic
17 juvenile idiopathic arthritis, which should
18 complete next year, and we'd hope to be back again
19 for that; and an additional program in the
20 cardiovascular area, where we've discovered -- and
21 this is a recent discovery -- that as with uric
22 acid crystals, cholesterol crystals can activate

1 this inflammasome mechanism and may be pathogenic
2 in atherosclerosis.

3 So we are looking at patients who have had a
4 first myocardial infarction and seeing if we can
5 reduce the risk of a second event. There is a
6 large mortality and morbidity study of over
7 7,000 patients which has started to enroll now and
8 will take us a few years to complete.

9 Canakinumab has the biological
10 characteristics on might expect of an IgG1
11 immunoglobulin. It's a potent anti-inflammatory,
12 and I've shown the data there of the 150-milligram
13 dose, which dramatically and rapidly resolves the
14 CRP elevations you get in acute inflammation. And
15 across a wide range of indications, we've looked at
16 many doses, but the 150 dose is the one which most
17 consistently reduces CRP very effectively and keeps
18 it at this plateau. It's the lowest of the doses
19 that has this dramatic effect across the broad
20 range of indications.

21 The indication that we propose is
22 canakinumab is an interleukin-1 beta blocker

1 indicated for the treatment of gouty arthritis
2 attacks in patients who cannot obtain adequate
3 response with nonsteroidal anti-inflammatory drugs
4 or colchicine. Ilaris has also been shown to
5 extend the time to next attack and reduce the
6 frequency of subsequent attacks.

7 We obtained approval in June 2009 for the
8 CAPS indication after a priority review as an
9 orphan indication. In November 2009, we had our
10 end-of-phase 2 meeting with the FDA around the
11 gouty arthritis program, and as a result of that
12 meeting, we had agreement at that time around the
13 population to study, the design of the phase 3
14 protocols, the dose selected for use in phase 3,
15 and the size of the safety database. We submitted
16 our BLA in February of this year, and that brings
17 us to this point in time.

18 This is our agenda of speakers today. In
19 addition, we have a number of scientific experts
20 who are very familiar with the details of the
21 program at your disposal. And you'll be hearing
22 from two of them, Dr. Larry Edwards and Dr. Bob

1 Wortmann, during the official presentations.

2 With that, I'd like to hand over to
3 Dr. Edwards to tell us about the unmet medical need
4 in gout. Thank you.

5 **Sponsor Presentation - Lawrence Edwards**

6 DR. EDWARDS: Thank you, Trevor. Good
7 morning, Ms. Chairman, members of the committee.
8 I'm Larry Edwards. I'm a consultant for Novartis,
9 and they paid for my transportation to this meeting
10 today.

11 What I'd like to do today is take those of
12 you that aren't familiar with gout on a little tour
13 of what the disease actually means. There are a
14 number of you on the panel that I know are gout
15 experts. I appreciate that, and no more expert
16 than a patient that suffers with it.

17 Gout is the most common inflammatory
18 arthritis by far. The most recent estimates from
19 the NHANES data places the number of people
20 suffering from this disease at about 8.3 million in
21 the United States. One of the cardinal features of
22 this disease is the characteristic agonizing pain

1 that comes on with the acute attacks that leads not
2 just to the severe pain but true functional
3 disability, and this persists for many days.

4 A subset of patients with this type of
5 attack is unable to take the standard therapies for
6 anti-inflammatory treatment of gout, and they
7 include the nonsteroidals as well as colchicine.
8 And this might be due to a relative or absolute
9 contraindication to these drugs, to intolerance of
10 them, or for simple lack of efficacy.

11 Glucocorticoids may be the only available
12 option. However, in high and persistent doses of
13 these drugs, given the types of patients that
14 develop gout, these can be problematic. Thus,
15 there is an unmet need in a subset of patients with
16 gout for a drug that would treat the inflammation
17 of the disease that has a different modality of
18 effect.

19 Over the next several slides, I'm going to
20 take you on the natural course of the disease for
21 those of you not familiar with it. Starting on the
22 left side, there is an antecedent period of

1 obligatory hyperuricemia that in males unusually
2 begins at about the time of puberty. In females,
3 hyperuricemia is prevented early on because of the
4 presence of estrogens, but through mid-life, with
5 lowering estrogens, the uric acid begins to
6 elevate, and then at the time of menopause will
7 attain the adult level of uric acid. The highest
8 level of uric acid at that time will approximate
9 those of males.

10 During this asymptomatic period of
11 hyperuricemia, the uric acid can precipitate out of
12 solution and deposit as microtophi in and around
13 joints. These have been demonstrated to be present
14 even before the very first attack of gout.

15 Then one day, usually several decades after
16 the beginning of hyperuricemia, we leave the period
17 of asymptomatic hyperuricemia and progress on into
18 the period of acute intermittent gouty arthritis.
19 And this is hallmarked by this middle section,
20 where there are spikes of pain, usually coming on
21 abruptly, no pain to maximum pain over a 10- to 12-
22 hour period. That level of pain plateaus out for

1 several days, 3 or 4 days, and then gradually
2 abates, even if untreated, over a period of another
3 3 to 4 days, for a total length of time of a very
4 painful episode of a week or more.

5 The joint itself that was involved returns
6 to a normal baseline, although the crystals
7 persist, and there is a low level of inflammation,
8 as evidenced by an increased number of white cells
9 in the joint, the presence of crystals, and
10 elevated cytokines.

11 Some period of time later, on average, about
12 11 months, a second attack occurs, maybe in a lower
13 extremity joint as before, maybe elsewhere, but the
14 pattern is very similar to that. And then over the
15 course of a decade or longer, these attacks become
16 more and more frequent. The duration of the
17 individual attacks is no longer the 7 days but will
18 stretch out to 10 to 14 days. And finally, just
19 after about 10 or 12 years, these may be as
20 frequent as occurring every month or two. 0

21 Then we enter into the final stage, and
22 that's now called advanced gout. It used to be

1 called chronic tophaceous gout. But because we
2 know that tophi are actually present throughout the
3 entire course here, that title is dropped.

4 In advanced gout, there is a progression of
5 the underlying arthritis to one of disability.
6 This is decidedly a destructive arthritis, with
7 overall disability similar to that of advanced
8 rheumatoid arthritis. But during this period of
9 time, there are also the acute painful flares that
10 we had seen in the earlier stages. It's during
11 this entire period of time that we are looking for
12 an alternative therapy for patients that can't
13 tolerate the current anti-inflammatory therapies
14 for gout.

15 How serious is this inflammation? In the
16 words of patients, it's very serious. In this
17 particular study of nearly 300 patients, 62 percent
18 described the typical attacks as being either
19 severe, very severe, or the worst pain imaginable.
20 And so on a visual analog scale of 100 milliliters,
21 that would take them from a 75 all the way up to
22 100. Okay?

1 A typical inflamed joint - this is the
2 typical podagra or acute first toe joint -- is
3 shown here. It can occur in other very painful
4 areas, including the midfoot, ankle, knees, and in
5 later attacks in virtually any peripheral joints,
6 including the hands, wrists, fingers.

7 In another survey of gout patients,
8 69 percent described the attacks as simply
9 miserable, with other very descriptive adjectives
10 of pain. But also you need to keep in mind that
11 there is a functional component to this pain. When
12 the pain is in the lower extremities, this means
13 the patients simply are not walking. They're not
14 able to get up out of their bed. If it's in the
15 upper extremities, they frequently have trouble
16 dressing. And this isn't a short-term pain. This
17 is over these many days that they're having the
18 acute attack of gout.

19 Complicating our treatment is the fact that
20 the gouty population is one that has many
21 comorbidities. I've listed six of the most common
22 ones up on the slide today, including hypertension,

1 hyperlipidemia, chronic kidney disease, coronary
2 artery disease, diabetes, and heart failure. This
3 is the subset of patients that we have to work
4 with, and it's the very reason that we difficulty
5 choosing drugs.

6 These comorbidities don't come singly. You
7 can see that from this figure on the right, that
8 3 percent have none of these comorbidities, and the
9 vast majority, 75 percent, will have either two,
10 three, or four of these together. And this is what
11 makes treatment tricky.

12 It's a significant disease. In this
13 particular survey of patients having three or more
14 attacks per year, 25 percent of them admit to
15 having gone to the emergency department for
16 purposes of treatment of their acute gouty
17 arthritis, and 15 percent have been hospitalized
18 for this condition. When hospitalized, they have
19 significant lengths of stay of about four days.
20 And if they develop gout during their
21 hospitalization, this adds another three days to a
22 long hospital course.

1 I'm going to review with you the currently
2 available therapies that we use in treating gout.
3 On this part of the slide, we're really discussing
4 the anti-inflammatory approach. And the standard
5 therapies that have been available for many decades
6 include the nonsteroidal anti-inflammatory drugs,
7 colchicine, and glucocorticoids. From these, there
8 are a number of problems. We use them roughly in
9 this order in this country, with nonsteroidals
10 giving the top nod, colchicine and glucocorticoids
11 in diminishing use.

12 The other side of treating gout, and the
13 more fundamental part, is getting at the uric acid
14 burden. And this, as you heard before, is really
15 going for the fundamental change. And there are a
16 number of drugs now available, but for decades, we
17 were stuck with two, allopurinol and probenecid.
18 Fortunately, that menu has been expanded over the
19 past several years to include febuxostat and
20 pegloticase because of unmet needs as well.

21 These two approaches together lead to the
22 optimal management of gout. The dotted line

1 connecting the reduced urate burden to inflammatory
2 pain control simply is a statement that, over time,
3 with adequate use of these urate-lowering drugs,
4 the number of flares, the painful component of
5 gout, will gradually resolve. And this is our goal
6 in every patient with gout.

7 This again lists the three most common anti-
8 inflammatory drugs, as well as some safety and
9 tolerability concerns for each of them, and then
10 the relevant comorbidities that these concerns
11 would interact with. And you can see, for
12 nonsteroidals, the problems with renal toxicity,
13 cardiovascular risks, and bleeding would certainly
14 be relevant in patients that had hypertension,
15 chronic kidney disease, or cardiovascular disease,
16 as well as a history of GI bleeds associated with
17 peptic ulcer disease.

18 Colchicine has well-known toxicities
19 including diarrhea, rhabdomyolysis, as well as
20 other neuromuscular problems and myelosuppression.
21 And these are particularly germane in patients with
22 chronic kidney disease and chronic liver disease.

1 And finally, glucocorticoids have problems with
2 hypertension, with worsening of glycemic control,
3 worsening of volume overload, as well as others
4 that would be both duration- and dose-related and
5 may be problematic in patients with hypertension,
6 diabetes, and cardiovascular disease.

7 So the subset of patients with frequent
8 gouty attacks that needs a new form of therapy are
9 those that did not receive adequate relief with
10 nonsteroidals and colchicine, that cannot tolerate
11 these drugs because of their well-known side
12 effects, or have a relative or absolute
13 contraindication to the nonsteroidals or
14 colchicine, most likely related to the
15 comorbidities that they're presenting with.

16 For these patients, glucocorticoids may
17 be -- they certainly are the only available other
18 option at this time, but there are frequently
19 concerns in groups of patients with using
20 corticosteroids frequently and in high doses.

21 So in summary, gouty arthritis is a chronic
22 inflammatory arthritis that features agonizing pain

1 and disability related to that pain. The greater
2 the frequency of the attacks, the greater the
3 burden of disease is.

4 A subset of patients with gouty attacks are
5 unable to obtain adequate response to nonsteroidals
6 and colchicine, and this may be because of
7 contraindications, intolerance, or lack of
8 efficacy, and glucocorticoids may be the only
9 available option at this time, and there are
10 concerns with these forms of therapy. Thus,
11 there's a need for a new set of drugs with new
12 mechanisms of disease that we can use in this
13 subset of patients with gouty arthritis.

14 Thank you for listening. I'll now bring up
15 Dr. Marjorie Gatlin.

16 **Sponsor Presentation - Marjorie Gatlin**

17 DR. GATLIN: Good morning, Dr. O'Neil,
18 members of FDA, and the committee. My name is
19 Marjorie Gatlin, and I am head of the
20 cardiovascular, metabolism, and inflammatory
21 diseases medical unit at Novartis. And I am here
22 with you this morning to discuss the dose selection

1 and efficacy of canakinumab in the treatment of
2 acute gouty arthritis.

3 At Novartis, we were very thoughtful about
4 the design of our program and the process by which
5 we share the dose. And I'd like to remind the
6 committee that the data I am presenting to you are
7 voting questions for you this afternoon.

8 In our program we demonstrated, in our
9 development program that was comprised primarily of
10 three trials in the treatment of acute gouty
11 arthritis, a phase 2 dose-selection trial and two
12 phase 3 trials with extensions, that canakinumab,
13 administered as 150 milligrams subcutaneously,
14 provided rapid and effective relief from the pain
15 and inflammation of an acute gouty arthritis
16 attack.

17 It is also effective in extending the time
18 to the next attack and reducing the risk of
19 subsequent attacks in a population with very
20 frequent gouty arthritis attacks. And canakinumab
21 efficacy is predictable in those patients that do
22 require retreatment.

1 I'm going to review with you this morning
2 the design of our phase 3 program; again, the
3 rationale for our dose selection; and then the
4 results of the program, including looking at the
5 co-primary endpoints of attack pain, delaying
6 subsequent attacks, as well as supportive secondary
7 endpoints; and then closing with looking at
8 efficacy in retreatment.

9 Our phase 3 program was comprised of two
10 replicate, identically designed clinical trials
11 conducted in patients with frequent gouty arthritis
12 attacks. In this program, we randomized patients
13 to receive canakinumab 150 milligrams when they
14 presented with an acute attack or the steroid
15 triamcinolone. We were thoughtful in our choice of
16 comparator. We chose not to use a placebo
17 comparator because we felt it was important to
18 assess the long-term benefits to these patients who
19 have prolonged gouty arthritis attacks and very
20 frequent attacks.

21 Patients, once randomized, received one of
22 the two study drugs and then were assessed for the

1 co-primary endpoint of pain intensity at 72 hours,
2 and then were followed for up to 12 weeks to assess
3 the second co-primary endpoint in terms of reducing
4 the risk of subsequent attacks. Eligible patients
5 could then enter a second 12-week extension trial
6 that was also blinded. In both the core and
7 extension trials, patients who suffered a
8 subsequent attack would be re-treated with a
9 randomized therapy.

10 I will share with you this morning data from
11 the 24-week treatment period on efficacy in
12 delaying subsequent attacks.

13 Eligible patients were then given the option
14 to enter into an open label extension trial, which
15 is currently ongoing. We did conduct an interim
16 analysis of that open label extension, and we have
17 safety data from those extension trials to share
18 with you this morning.

19 Our two clinical trials were both
20 randomized, double-blind, with the active
21 comparator. Both study drugs of canakinumab or
22 triamcinolone were administered by study site

1 personnel. If a patient had a subsequent attack,
2 these attacks were to be re-treated within five
3 days of the onset of that attack, but only after 14
4 days had elapsed from their last dose of study
5 medication.

6 We did allow rescue medication that could be
7 administered after the first pain assessment at
8 six hours, and was to be withheld within four hours
9 of subsequent pain assessments. The allowed rescue
10 medications were oral steroids, acetaminophen, or
11 codeine.

12 In our program, we enrolled adult male and
13 female patients who had chronic gouty arthritis,
14 and this was a population of patients with very
15 frequent gouty arthritis attacks. They were
16 required to have at least three attacks in the
17 previous year. They had to present to the
18 investigator within five days of the onset of that
19 baseline attack. And the attacks were all required
20 to be painful, registering greater than
21 50 millimeters on a visual analog pain scale.

22 We studied the population for whom we are

1 seeking this indication, a population of patients
2 who had a relative or absolute contraindication to
3 NSAIDs or colchicine, those that were intolerant of
4 or had previously experienced lack of efficacy with
5 these agents. We excluded patients who were taking
6 specific pain relief medications; those using the
7 biologics anakinra, riloncept, or others; those
8 patients with severe renal impairment; and those
9 with active or recurrent infections.

10 We had two co-primary endpoints in both of
11 our phase 3 trials. The first co-primary was an
12 assessment of pain intensity in the most affected
13 joint at 72 hours, and the trial was powered to
14 detect a 12 millimeter difference on the visual
15 analog scale. We also had a second co-primary
16 looking at the time to the first new attack, and
17 the study was powered to detect a relative risk of
18 .415. It is important to note that success
19 requires statistical significance for both primary
20 endpoints, and the overall power for each trial was
21 greater than 90 percent.

22 Now I'd like to discuss the dose rationale

1 for phase 3. These are patients who are
2 experiencing very painful attacks, and in the
3 treatment of pain, it is important to get right on
4 top of that pain and provide these patients with
5 fast and adequate pain relief.

6 In our phase 2 dose-ranging program, we
7 studied a wide range of doses with over a tenfold
8 difference between our lowest dose of 10 milligrams
9 and the top dose studied of 150 milligrams to the
10 active comparator, triamcinolone. We studied 200
11 adult patients with acute gouty arthritis attacks
12 who also have contraindications to, intolerance of,
13 or lack of efficacy to NSAIDs and colchicine.

14 In this program, we demonstrated that the
15 150-milligram dose provided the most rapid and
16 effective relief of the pain of these very painful
17 gouty arthritis attacks, being significantly
18 different from other doses of canakinumab and
19 triamcinolone. As you can see depicted on this
20 slide, as early as 24 hours, there was
21 statistically significantly better response in
22 terms of pain relief for these patients, as early

1 as 24 hours, that was maintained throughout the
2 7-day observation interval.

3 Because the question has been raised about
4 whether or not a lower dose would have been as
5 effective, I'd like to share with you some specific
6 data looking at the comparative efficacy of 150
7 versus the next lowest dose we studied, which is
8 90.

9 On this slide, you can see we compared the
10 relative efficacy of the two doses to the steroid
11 comparator. In the light blue, you can see the
12 benefit accrued with canakinumab 150 milligrams in
13 terms of pain relief versus the steroid comparator
14 over the entire 7-day observation period.

15 I would like to direct your attention to the
16 early time points, where you can see that there was
17 a clinically significant benefit versus a steroid
18 comparator as early as six hours, and these
19 differences achieve statistical significance at
20 24 hours.

21 In contrast, the 90-milligram dose of
22 canakinumab did not provide consistent benefit over

1 the steroid comparator, and in fact, at no time
2 point was it significantly better than the steroid
3 comparator. And at 6 and 12 hours, it was
4 undifferentiable (ph) from the steroid comparator.

5 When we looked at the safety data that we
6 considered in terms of dose selection, we saw that
7 the safety for the 150-milligram dose was not
8 differentiable from lower doses. You can see the
9 150-milligram dose here highlighted in blue, as
10 well as that of the steroid comparator.

11 There was no dose response for serious
12 adverse events; in fact, there were no serious
13 adverse events reported in patients receiving 150.
14 There was no dose response for overall adverse
15 events. There were no patients who discontinued
16 for an adverse event. And the risk of having an
17 adverse event related to infection was low and
18 constant across all doses.

19 Now I'd like to share with you the results
20 of our phase 3 program. We conducted the two
21 phase 3 trials. The 2356 trial was the trial that
22 was conducted outside the United States. And in

1 this program, we randomized 230 patients equally to
2 canakinumab and triamcinolone. Most of the
3 patients completed, successfully completed, the
4 12-week core trial.

5 As you can see here, there was one patient
6 who died in the triamcinolone group during the core
7 trial. The results of what happened with that
8 patient will be discussed in detail during our
9 safety presentation. Three-quarters of the
10 patients then went on to enter the 12-week double-
11 blinded extension period, and the majority of those
12 patients also successfully completed six months of
13 therapy.

14 In the North American trial, 2357, again we
15 randomized equally approximately 230 patients to
16 canakinumab or the steroid comparator. In this
17 trial, there was one death during the 12-week core
18 trial period on canakinumab. And, again, that
19 patient will be discussed in detail during the
20 safety presentation.

21 The majority of patients successfully
22 completed the core trial, and the majority of those

1 patients went on to enter the extension trial and
2 finished that, providing us with six months worth
3 of data.

4 When we look at the demographics and
5 characteristics of our population, we enrolled a
6 population of patients with very frequently
7 occurring gouty arthritis attacks that is
8 representative of the overall population that
9 Dr. Edwards has just discussed with you. These
10 patients were predominately male and middle-aged.
11 The mean BMI was approximately 32.

12 While the patients enrolled in our program
13 were predominately Caucasian, I would like to draw
14 your attention to the fact that in the H2357 trial
15 conducted in North America, we did have one-fifth
16 of the patients enrolled who self-identified as
17 black. Approximately half the patients in the
18 program had more than one joint affected, and on
19 average, the serum urate levels were elevated in
20 this population of frequently flaring patients.

21 As Dr. Edwards has mentioned to you, all
22 patients with gout have tophi on some level, and we

1 did have a proportion of patients that actually had
2 visible tophi. These were very painful attacks.
3 If you look at the bottom of the slide, you'll see
4 that the mean baseline pain score on the visual
5 analog scale was approximately 75, which is
6 characterized as very severe pain. And this is a
7 population of patients with very frequent attacks.
8 As a reminder, we enrolled patients who had at
9 least three attacks per year; but in fact, on
10 average, patients reported six and a half to seven
11 attacks in the previous year.

12 As we mentioned before, we studied a
13 population of patients that have a significant
14 unmet need. Ninety percent of the patients
15 enrolled in our program reported a contraindication
16 to, intolerance of, or previous lack of efficacy to
17 NSAIDs; 42 percent a contraindication to,
18 intolerance, or previous lack of efficacy to
19 colchicine; and one-third reported that to both
20 NSAIDs and colchicine.

21 This is a highly comorbid patient
22 population, as Dr. Edwards discussed with you, and

1 the population that we enrolled in our program is
2 representative of the overall gouty arthritis
3 population. Eighty-four percent of the patients in
4 the canakinumab group reported at least one
5 comorbidity or cardiovascular risk factor at
6 baseline, with the most common risk factors being
7 hypertension and obesity, with a representative
8 sample of patients who had dyslipidemia and
9 metabolic syndrome and diabetes. I'd like to call
10 your attention to the fact that we had 14.7 percent
11 of the canakinumab patients with chronic kidney
12 disease, slightly more than in the triamcinolone
13 group.

14 Now I'd like to address the co-primary
15 endpoints. What we found in our two replicate
16 phase 3 trials is that canakinumab was superior to
17 the steroid comparator on both co-primary endpoints
18 of reducing the pain of an attack and reducing the
19 risk of subsequent attacks. When one looks at the
20 pain intensity at 72 hours, the difference versus
21 triamcinolone in the 56 trial conducted outside the
22 U.S. was a change of 11.4, and in the U.S. trial,

1 it was 9.8, highly statistically and clinically
2 significant in both cases.

3 Similarly, there was a significant reduction
4 in the risk of an attack over the 12-week period of
5 the core trial, with a 55 percent risk reduction in
6 the 56 trial and a 68 percent risk reduction in the
7 2357 trial, again both highly statistically
8 significant.

9 Now I'd like to share with you some further
10 detail on these endpoints. As Dr. Edwards
11 mentioned, these attacks go on for many, many days,
12 so it's important to consider not just the pain
13 relief at 72 hours but to consider the rapidity
14 with which this pain relief is achieved for these
15 patients and how it is sustained.

16 As you can see in this graph, we are looking
17 at the pain intensity on the visual analog scale
18 from a baseline of 74 in the 2356 trial. And you
19 can see that canakinumab, in blue, provided very
20 rapid and effective pain relief that was
21 significantly better from the comparator as early
22 as 12 hours, and the benefit was maintained over

1 the full seven days of the observation period.

2 Similarly, in the U.S. trial, again from a
3 baseline of 74, you can see that there was very
4 rapid and effective pain relief over the full 7-day
5 interval that was statistically significantly
6 different at 48 hours but was clinically meaningful
7 as early as 6 hours.

8 When we look at the Kaplan-Meier curves at
9 reducing the risk of subsequent attacks in this
10 population that had very frequent attacks, looking
11 at the cumulative rate of new attacks on the Y
12 axis, you can see that the curves separate very
13 early, and throughout the 12-week interval there
14 was a 55 percent reduction in the risk of a new
15 attack. And similarly, in the H2357 trial, the
16 curves separate very early, and there is a well-
17 maintained reduction risk that is, overall,
18 68 percent reduction at 12 weeks.

19 Now, when we look at secondary analyses that
20 also inform the profile of this product, it's
21 important to assess how many patients have
22 successful response to treatment. A 30 percent

1 reduction from baseline is considered a moderate
2 response, and a 50 percent reduction in baseline
3 pain is considered a substantial response.

4 In both the 2356 trial, seen here, and the
5 2357 trial, you can see for all levels of response,
6 canakinumab was superior to the steroid comparator
7 in providing relief from these painful gouty
8 arthritis attacks. In fact, 84.6 percent of
9 canakinumab patients in the 56 trial and
10 86.9 percent of patients in the 57 trial
11 experienced moderate pain relief at 72 hours, and
12 approximately 64 percent in the 2356 trial, and
13 79 percent of patients experienced substantial
14 relief at 3 days.

15 This pain relief was also associated with
16 clinically meaningful improvements in clinical
17 signs of inflammation. There were more patients in
18 both trials who experienced resolution of their
19 pain, and more patients in both trials who had
20 resolution of the tenderness and swelling of their
21 affected joints.

22 Similarly, there was less use of rescue

1 medication in patients who were randomized to
2 canakinumab. Two-thirds of canakinumab patients
3 overall in the program did not require rescue
4 medication, statistically significant compared to
5 triamcinolone.

6 Importantly, I'd like to draw your attention
7 to the use of oral steroid rescue medication. In
8 both trials, more than twice as many triamcinolone
9 patients took rescue medication with oral steroids
10 compared to that with canakinumab.

11 Now, it's important also to look at the
12 prolonged effect in terms of reducing the risk of
13 gouty arthritis attacks in a frequently flaring
14 population. When we look at the data from the core
15 and extension trial together -- and a reminder,
16 both trials were double-blind -- looking at the
17 cumulative risk of attacks, the separation that we
18 observed early in both trials was maintained
19 throughout the 24-week follow-up period, with a
20 52 percent reduction in the 56 extension trial and
21 a 60 percent reduction in the 57 extension trial,
22 both of which were highly clinically meaningful and

1 statistically significant.

2 In fact, when we look in greater detail at
3 reducing the attack burden on these patients, you
4 can see that in the patients that did have new
5 attacks, the mean number of attacks per patient was
6 half or less than half in canakinumab patients
7 compared with steroid patients, and this difference
8 was statistically significant.

9 Two-thirds of the patients, or 72 percent,
10 were attack-free for a full six months. And when
11 we look at the number of attacks per patient, you
12 can see that for every level of attack, be it one
13 attack, two attacks, three or more attacks, there
14 were significantly fewer, or fewer canakinumab
15 patients, with new attacks than those who had been
16 randomized to the steroid treatment.

17 Now, it's important to think about efficacy
18 and retreatment in that population of patients that
19 did require retreatment. On this slide, I'd like
20 to draw your attention to the fact that in those
21 canakinumab patients that required retreatment, the
22 mean number of attacks in the last year was greater

1 than in the overall population, with a report of
2 8.1 attacks in the previous year for those patients
3 who had subsequent attacks and required
4 retreatment.

5 Importantly, the efficacy of canakinumab in
6 treating subsequent attacks is predictable. For
7 those patients that had a substantial benefit when
8 treating the baseline attack -- that is, they had
9 at least a 50 percent reduction in pain for the
10 treatment of that baseline attack -- for subsequent
11 attacks, they had a similarly effective and
12 substantial pain response. And in those patients
13 that did not have a substantial response to the
14 baseline attack, that was also seen with subsequent
15 treatments. So the efficacy is predictable for
16 future use.

17 Overall, greater than 80 percent of patients
18 on canakinumab can expect a major benefit. At
19 12 weeks, we had 77 percent of patients with a dual
20 benefit in that they had substantial pain relief
21 and no new attack for 12 weeks. Additionally,
22 there were 6 percent of patients in that core trial

1 who had substantial pain relief for their baseline
2 attack, and while they may have had a subsequent
3 attack, they continued to have substantial pain
4 relief with every treatment.

5 At 24 weeks, we continued to have over
6 80 percent of patients with a substantial benefit.
7 Sixty-five percent at that point had a substantial
8 benefit in terms of pain reduction and had no
9 attacks for six months, and 17 percent of patients,
10 while they had a subsequent attack during this
11 period, continued to experience substantial pain
12 relief with every new attack.

13 So, in summary, we have clearly demonstrated
14 that the 150-milligram dose provides the rapid and
15 effective pain relief and reduction of attacks that
16 these patients require. We demonstrated superior
17 efficacy by providing more rapid and sustained pain
18 relief, and two-thirds of canakinumab-treated
19 patients did not require rescue medication.

20 We significantly delayed the risk of having
21 a new attack with canakinumab, with 72 percent of
22 patients remaining attack-free for six months. And

1 it's important for physicians to know that
2 canakinumab is as efficacious in treating the last
3 attack as it was the baseline attack, and the
4 efficacy in treating pain on the baseline attack is
5 predictive of future responses.

6 Now I'll turn you over to my colleague,
7 Dr. Michael Shetzline, who will review safety.

8 **Sponsor Presentation - Michael Shetzline**

9 DR. SHETZLINE: Thank you, Dr. Gatlin.

10 Dr. O'Neil, advisory committee members, FDA,
11 I'm Michael Shetzline. I'm the global program head
12 for the canakinumab team, and I'd like to present
13 today the critical safety information that's part
14 of our submission dossier that ensures safe
15 treatment of patients with gouty arthritis with
16 canakinumab.

17 It's important to understand, and as was
18 highlighted by the agency, that the use of
19 canakinumab for gouty arthritis follows our CAPS
20 approval. And in our CAPS program, we have
21 patients who have received canakinumab for up to
22 five years at every 8-week dosing intervals at the

1 150-milligram dose form.

2 Nonetheless, within the gouty arthritis
3 program, we have seen safety events, and we need to
4 be mindful from the healthcare provider's
5 perspective that these events are real, we need to
6 be informed about them, and we need to also, as we
7 look at the data, understand that they were
8 reversible, that patients recovered, and by and
9 large, these can be managed appropriately by the
10 physician.

11 This is an overview of the safety
12 presentation I'll perform today. We'll start with
13 the safety population. We'll then move to the
14 safety profile, specifically, the adverse events,
15 the serious adverse events, infections,
16 cardiovascular events, and malignancies. And then
17 we'll move to safety areas of special interest,
18 immunogenicity, hypertension, renal function,
19 neutrophils, other lab abnormalities, and safety on
20 retreatment, and then summarize and provide some
21 safety recommendations.

22 Our safety data set comes from three

1 critical sources: the gouty arthritis data set,
2 the rheumatoid arthritis data set, and the approved
3 indication CAPS. The gouty arthritis data set
4 provides us information from phase 2 and phase 3 in
5 the target population with an active control, and
6 clearly, the active control in this safety data set
7 is triamcinolone. In addition, we have open label
8 long-term data from our extension trials, and this
9 gives us information for long-term safety and
10 retreatment.

11 Now, critically, we have the safety data
12 from the rheumatoid arthritis data set, and this a
13 data set that has received higher doses of
14 canakinumab, up to 150 and 300 milligrams every 2
15 to 4 weeks, and in some cases proceeded by a
16 600-milligram IV loading dose. This data provides
17 us very critical information in a placebo-
18 controlled fashion because, as I mentioned, the
19 phase 3 program had an active control. And, in
20 addition, we have long-term data in rheumatoid
21 arthritis in patients who have had these high doses
22 for up to 144 weeks.

1 Finally, as I mentioned, we have our CAPS
2 program, where these patients have received
3 150 milligrams every 8 weeks. We have up to five
4 years of follow-up in certain patients, and this is
5 our postmarketing data set.

6 So looking at the exposure in our gouty
7 arthritis data set on the left and our rheumatoid
8 arthritis data set on the right, you can see, in
9 gouty arthritis, in total, we have 691 patients who
10 have received canakinumab in gouty arthritis. And
11 at the 24-week or 6-month period, we have 140
12 patients receiving a 150-milligram dose. In
13 addition, we have 332 patients receiving
14 canakinumab at six months in the rheumatoid
15 arthritis data set.

16 At the 1-year period, we have 74 patients in
17 the canakinumab treatment group versus 255 in the
18 canakinumab group for rheumatoid arthritis. And,
19 again, these are the rheumatoid arthritis doses of
20 150 to 300 milligrams every 2 to 4 weeks.

21 This slide shows you the patient
22 characteristics of our safety population from the

1 phase 3 program. And, in general, the populations
2 were well-balanced. There was somewhat more
3 frequent use of urate-lowering therapy in the
4 triamcinolone group, and somewhat more patients who
5 had contraindications to both NSAIDs and colchicine
6 in the canakinumab group.

7 Comorbidities, as Dr. Gatlin alluded to
8 earlier, were fairly well-balanced. However, there
9 were a few more frequent dyslipidemic patients in
10 the triamcinolone-treated group versus a few more
11 metabolic syndrome patients in canakinumab. There
12 were patients reported with chronic kidney disease
13 more prevalent in canakinumab at 15 percent versus
14 10 percent for triamcinolone. And as you can see
15 at the bottom part of this table, there are a few
16 more frequent cardiovascular comorbidities in the
17 canakinumab-treated population.

18 I'd now like to move to the safety profile.
19 Looking at this table, these are the adverse events
20 reported by greater than or equal to 2 percent of
21 patients in the gouty arthritis phase 2 and phase 3
22 program.

1 You can see, for infections, there were
2 notable increases in the canakinumab-treated group
3 compared to triamcinolone. In the musculoskeletal
4 category, there were more frequent reports of back
5 pain and OA for canakinumab. For the gout and
6 muscle spasms, these were reported more frequently
7 for triamcinolone.

8 In addition, we have increases in
9 hypertriglyceridemia and hypercholesterolemia lab
10 abnormalities in the canakinumab-treated group.
11 And finally, GGT elevations were noted more
12 frequently in the canakinumab-treated group. We
13 will discuss those events more completely in the
14 safety presentation.

15 I'd like to now review the phase 2/3 program
16 deaths, SAEs, and AEs. And you can see at a
17 relatively similar exposure, 96.5 years for
18 canakinumab versus 97.3 years for triamcinolone,
19 there were more reports of one serious adverse
20 event in the canakinumab-treated group,
21 7.1 percent, versus 3.1 percent for triamcinolone.
22 The deaths were well-balanced. These percentages

1 represent 1 case in each group. There were more
2 infectious SAEs reported, 1.6 percent for
3 canakinumab versus none in triamcinolone. That
4 1.6 percent represents for SAEs of infection.

5 In addition, there were few discontinuations
6 due to adverse events, 0.8 or 2 events for
7 canakinumab versus none for triamcinolone. And
8 there were 19.4 percent of infectious AEs reported
9 for canakinumab versus 12.9 percent in
10 triamcinolone. And we will review the infectious
11 events more completely in the presentation.

12 In comparison from the rheumatoid arthritis
13 data set, using the higher doses exposed in the
14 gouty arthritis data set, we can see the SAEs and
15 AEs here. Notably, at the 150-milligram dose,
16 there are 15.8 patient years exposure compared to
17 40.6 in placebo. But, importantly, we have 96.5
18 patient years exposure in the greater-than-150-
19 milligram arm, representing 263 patients.

20 You can see patients reporting at least one
21 SAE from the rheumatoid arthritis data set. There
22 was one, actually, patient in this reported group

1 versus nine in placebo, or 1.4 percent versus 7.4
2 percent. And there were 12, or 4.6 percent, in the
3 greater-than-150-milligram arm.

4 There were no deaths reported during the
5 placebo-controlled phase of the RA data set, and
6 infectious AEs, you can see here, were not reported
7 in the 150-milligram canakinumab group, nor in
8 placebo. There were seven events or 2.7 percent of
9 patients reporting infectious AEs at the greater
10 than 150 milligram dose. You can see the data for
11 at least one AE, discontinuations due to AEs, and
12 infectious AEs on the bottom of this curve, or
13 table.

14 Now, I'd like to review a little more
15 closely the deaths in the gouty arthritis phase 2
16 and phase 3 and additional RA data sets. There
17 were 9 deaths reported in the gouty arthritis and
18 RA clinical trials. There were 3 deaths in the
19 gouty arthritis controlled studies, 3 in the gouty
20 arthritis open label long-term extensions, and 3 in
21 the rheumatoid arthritis open label extensions.

22 One of note in the gouty arthritis control

1 data set was a 63-year-old receiving canakinumab
2 who had an intracranial hemorrhage. This patient
3 had known hypertension, renal disease, and thyroid
4 disease with depression and epilepsy, which is not
5 shown up in this slide, but the "with" is with
6 depression and epilepsy.

7 From the gouty arthritis open label long-
8 term extensions, there was one case of pneumonia.
9 There was a 74-year-old who had known COPD and
10 congestive heart failure. This patient was on
11 inhaled steroids and had an initial pneumonia and
12 then a subsequent pneumonia and had a fatal event.
13 She also had significant kidney disease.

14 There was a 67-year-old who had a sudden
15 death. This patient had known significant and
16 severe cardiovascular disease. He had a prior MI,
17 congestive heart failure, myocardial fibrosis, and
18 dysrhythmias. His ischemic heart disease and
19 myocardial fibrosis was confirmed at autopsy.

20 In the RA open label period, we had one
21 patient who had a wound infection status post an
22 intestinal rupture in a 60-year-old with known

1 hypertension in the rheumatoid arthritis studies on
2 methotrexate. And there was one patient who had
3 metastatic lung cancer, a 70-year-old with known
4 chronic obstructive pulmonary disease who was an
5 active smoker, emphysema, additionally on
6 methotrexate for rheumatoid arthritis.

7 These deaths are consistent with what could
8 be expected for this comorbid gouty arthritis
9 patient population.

10 I'd like now to give a high-level review of
11 the leading nonfatal serious adverse events per
12 patient. There were three cardiovascular
13 disorders, and we'll talk more about them when we
14 go through the cardiovascular adverse events.
15 Similarly, there were two or three events for other
16 reporting categories, and notably, the three
17 infections and infestations we will talk about as
18 well.

19 So I'd like to look more closely at the
20 11 subjects throughout the phase 2/phase 3 gouty
21 arthritis data set. This is all canakinumab doses.
22 There were 11 subjects with serious infectious

1 events. We have already spoken about one of these,
2 the pneumonia, the patient on inhaled steroids who
3 had two pneumonias in a setting of canakinumab use
4 who had a fatal event in the long-term extension.
5 I'd now like to highlight the three serious adverse
6 events from our phase 3 program.

7 There was a 52-year-old male receiving
8 150 milligrams of canakinumab who had a jaw
9 abscess. This jaw abscess occurred in a setting of
10 decreased neutrophil counts, and we'll talk more
11 about that when we talk about infections and
12 decreased neutrophil counts. This patient did have
13 a jaw abscess. He was treated with antibiotics,
14 had an irrigation and drainage, and made a complete
15 recovery.

16 There was a 26-year-old male who had an
17 abscess in the forearm. He was treated with
18 antibiotics and made a full recovery. And there
19 was one patient who had a gastroenteritis, who
20 actually had this after a lap gastric banding
21 procedure, who also made a full recovery.

22 It's important to understand that of these

1 11 serious infectious adverse events, with the
2 exception of the pneumonia case who I identified
3 earlier on, all made a complete recovery and were
4 able to respond to standard of care therapy. In
5 addition, there were no confirmed cases of
6 opportunistic infections, including tuberculosis.

7 I'd now like to take a specific look at the
8 cardiovascular events that have been reported. As
9 noted, there were four events in canakinumab versus
10 one in triamcinolone. In our gouty arthritis data
11 set, we did a very thorough review of
12 cardiovascular events. We had a cardiovascular/
13 cerebrovascular events review team, which were
14 externals. They reviewed all events that were
15 consistent with any major adverse cardiac event
16 terms. And in that review, they identified a few
17 cases of cardiovascular events, which are shown on
18 the bottom of this table.

19 There were two events reported for
20 canakinumab versus two in triamcinolone. So the
21 output of this major adverse cardiac event review
22 demonstrated consistent reporting across

1 canakinumab and triamcinolone.

2 Now, I'd like to move to malignancies.
3 There were two malignancies reported in the gouty
4 arthritis phase 2/3 program, and they are shown
5 here. There was one prostate cancer in the
6 canakinumab group receiving greater than
7 200 milligrams of canakinumab, and there was one
8 renal cancer in the colchicine-treated group.

9 We also, as I mentioned, have longer-term
10 data for the use of canakinumab in rheumatoid
11 arthritis. And you can see, of the eight
12 malignancies reported in the rheumatoid arthritis
13 data set, there were no chronicity or increased
14 reporting of malignancies with longer duration of
15 therapy for the high doses used in the rheumatoid
16 arthritis program, again, 150 to 300 milligrams
17 every 2 to 4 weeks.

18 So, in summary, fatal events were balanced
19 across treatments and consistent with underlying
20 comorbidities. SAEs and infectious SIEs were
21 reported with canakinumab and are consistent with
22 the mechanism of action of canakinumab. Serious

1 infectious events did respond to standard of care
2 with the one exception, the complicated patient
3 with multiple comorbidities who was also
4 additionally on inhaled steroids. Major adverse
5 coronary events were balanced across treatments,
6 and there was a low and balanced incidence of
7 malignancies.

8 I'd now like to turn attention to critical
9 areas of importance; these are areas we call "of
10 special interest," specifically immunogenicity,
11 hypertension, renal function, neutrophils; and then
12 lab abnormalities, hyperlipidemia, liver function
13 test, and uric acid, and then evaluate the critical
14 area of safety on retreatment.

15 For immunogenicity within the gouty
16 arthritis data set, we did a thorough review of
17 anaphylactic or hypersensitivity type reactions,
18 and there were no subjects with confirmed
19 anaphylaxis by review with the Sampson criteria.
20 There were no severe injection site reactions
21 reported as adverse events. There was one moderate
22 and two mild adverse events reported in the

1 canakinumab 150-milligram arm. There was one
2 subject who did demonstrate PK changes in a setting
3 of loss of efficacy; however, this patient did not
4 develop anti-canakinumab antibodies.

5 For the anti-canakinumab antibody assays, we
6 identified 1.1 percent positive at the end of
7 study. These were of low titer and primarily in
8 phase 2. There were no PK abnormalities or
9 immunogenicity-related adverse events reported.

10 In the all-RA data set, similarly we did a
11 thorough review with the Sampson criteria, and
12 there were no confirmed anaphylaxis events. And no
13 patient in the RA program was identified with anti-
14 canakinumab antibodies. For the CAPS program,
15 we've seen no immunogenicity or anaphylactoid
16 reactions to date.

17 So the low rate of immunogenicity to date is
18 important to understand; however, continued
19 observation is warranted given our current data
20 set.

21 For blood pressure within the phase 2/3
22 program, you can see the changes from baseline for

1 systolic blood pressure and diastolic blood
2 pressure here. The systolic blood pressure changes
3 of at least one measurement of greater than
4 140 millimeters of mercury were reported more
5 frequently in triamcinolone, 28 percent, versus
6 25 percent for canakinumab. The mean change for
7 both groups, however, was reduced blood pressure by
8 about 2 millimeters of mercury. For diastolic
9 blood pressure changes, they were more frequently
10 reported in canakinumab, 30.2 percent versus 26.5
11 for triamcinolone. And the mean changes here were
12 negligible.

13 In addition, we've looked at worsening of
14 hypertension in patients with baseline
15 hypertension, and there was no worsening of
16 hypertension in patients with baseline hypertension
17 receiving canakinumab.

18 In terms of renal function, we looked at any
19 change post-baseline by creatinine clearance by the
20 Cockroft-Gault evaluation. And you can see
21 relatively similar reporting, with 10.7 percent for
22 canakinumab versus 8.7 for triamcinolone. And in

1 terms of sustained changes from baseline where the
2 creatinine clearance is greater than 1.5 or the GFR
3 was reduced by 25 percent at all post-baseline
4 visits, there were four events reported for
5 canakinumab versus three for triamcinolone.

6 We did a more complete look at the renal
7 function in terms of change for baseline in
8 patients with chronic kidney disease at baseline.
9 And you can see in this slide that GFR, as
10 calculated by MDRD -- and this is change from
11 baseline -- for canakinumab, there was an
12 improvement, or probably a stable event in terms of
13 a 4 mLs per minute increase in GFR for canakinumab
14 versus roughly 1 to 2 for triamcinolone.

15 We looked a little further in terms of
16 microalbuminuria, another index of renal function,
17 and there was no clear negative impact in terms of
18 microalbuminuria for canakinumab treatment. If
19 anything, the microalbuminuria went in a positive
20 direction.

21 We looked more closely because we did have
22 the chronic rheumatoid arthritis-treated patients,

1 again, higher dose treatments for a much longer
2 period of time. This is the placebo data, so much
3 more relevant to the higher dose than the longer
4 period of time.

5 The creatinines across two canakinumab
6 treatment arms, the 150 or the greater-than-150
7 arm, you can see in this graph those changes were
8 consistent with those found with placebo.
9 Similarly, looking at GFR, there was a small change
10 in GFR in terms of a negative direction, but this
11 was consistent between the two canakinumab-treated
12 groups, 150 and greater than 150, with placebo in
13 this placebo-controlled data set.

14 Finally, we looked at the rheumatoid
15 arthritis long-term data to look for creatinine
16 clearance changes over the two to three years of
17 this reporting period. And you can see with longer
18 exposure in the rheumatoid arthritis data set,
19 there is no increased reporting of increases
20 in creatinine clearance with exposures of high-dose
21 canakinumab out to 2 to 3 years.

22 Now, there were three reports of renal

1 failure from the gouty arthritis data set. One,
2 the top one, was from our phase 3 program, and two
3 were from the phase 2 program. It's important to
4 understand that all three of these cases came in
5 with renal insufficiency or renal dysfunction at
6 baseline. And it's also important to understand
7 that they all recovered to their baseline levels.

8 One was a 73-year-old with a history of
9 renal insufficiency and hypertension. She was
10 hospitalized dehydrated, was treated with
11 rehydration and antibiotics for her UTI, and she
12 made a complete recovery.

13 There was one patient, a 44-year-old man,
14 who sadly had a significant nephrotic syndrome at
15 baseline and probably should not have been enrolled
16 in a study, but was enrolled in a study. He did
17 have worsening of renal function and did not
18 respond till he was treated with steroids for his
19 nephrotic syndrome. After treatment, he did make a
20 recovery to his renal function to baseline.

21 Finally, we have a 64-year-old male who also
22 did have renal insufficiency at baseline who had

1 some abnormal renal tests throughout the study.
2 His renal function did return to baseline and he
3 completed the study as planned.

4 I'd now like to turn to neutrophil counts
5 and look specifically at the CTC grade for
6 neutropenia in the study population. You can see
7 we've studied -- the three doses are shown here for
8 canakinumab versus the triamcinolone and colchicine
9 comparators. The majority of these neutrophil
10 decreases were grade 1, as you can see shown here.
11 And importantly, there were no cases of grade 4
12 neutropenia found in the 150-milligram arm of
13 canakinumab.

14 Now, we did find two events of transient
15 decreases in neutrophil counts in the greater-than-
16 200-milligram of canakinumab treated. And it's
17 also important to understand that these two
18 transient decreases were noted from the same site
19 on the same day, and both were repeated, and on
20 redraw and repeat 6 days later were back to their
21 pre-normal levels prior to this noted one event of
22 a decrease.

1 Within the phase 3 program, we have looked
2 closely at the chronicity of the neutrophil counts
3 in the gouty arthritis data set. And you can see,
4 triamcinolone is on the yellow at the top, and you
5 can see with triamcinolone you get a transient
6 increase in the neutrophil count. We should
7 realize that the baseline or the time zero here is
8 in the setting of active inflammation for a gouty
9 arthritis flare. So these neutrophil counts will
10 be high at that baseline period.

11 But you can see nonetheless that there is a
12 decrease in neutrophil count that is manifest with
13 canakinumab treatment. This is a decrease even in
14 the setting of the elevated neutrophil count that
15 would be happening in the inflammatory state. But
16 you can see, with time, the neutrophil counts do
17 normalize towards the triamcinolone, which we would
18 consider the normal values, out to around 80 to
19 112 days.

20 Now, we looked at the rheumatoid arthritis
21 data set to better understand if there's any
22 negative consequences to longer-term high-dose

1 exposures to canakinumab in neutrophil counts. And
2 you can see, importantly, in this slide that the
3 grade 1 neutropenia was found at roughly a
4 5 percent level, and again, confirming that there
5 were no reports of grade 4 neutropenia, which is
6 the clinically most relevant category for
7 neutropenia, even out to 2 to 3 years' exposure of
8 canakinumab at 150 to 300 milligrams every 2 to
9 4 weeks.

10 Now, we do also have data for the neutrophil
11 counts from the rheumatoid arthritis placebo-
12 controlled program and show that here. You can see
13 the placebo line is the flat line, and you can see
14 there was a transient decrease, even compared to
15 placebo, in the neutrophil counts in the RA data
16 set. And this neutrophil count did come back
17 towards the placebo level out to 12 weeks, so a
18 reversible condition in this population.

19 Now, there were two cases, and I'd like to
20 discuss those further here, of patients who had
21 neutropenia and an infection. One was a patient, a
22 58-year-old male, who had a normal white count at

1 baseline. He subsequently developed a low absolute
2 neutrophil count and white count on day 29. He had
3 a respiratory tract infection on day 131, which was
4 reported by the physician as mild. He did improve
5 with antibiotics, his blood counts normalized, and
6 he completed the study as planned, so a complete
7 recovery. You can see his counts in the table
8 below.

9 Also, there was one case from our phase 3
10 program, a 52-year-old male who I mentioned to you
11 earlier. This was one of our serious adverse
12 events that we reported earlier in the
13 presentation. This patient -- we don't have the
14 baseline values for neutrophils, but this patient
15 did have low neutrophil counts on day 4 and day 58.
16 This patient did develop a jaw abscess on day 29 in
17 the setting of his low neutrophil counts. He did
18 improve with antibiotics, irrigation, and drainage,
19 and he made a complete recovery.

20 So now I'd like to turn to some other
21 notable lab abnormalities: hyperlipidemia, liver
22 function tests, and uric acid.

1 If we look at the lipid profiles across the
2 phase 2/3 program, you can see some changes between
3 the canakinumab-treated group and triamcinolone.
4 The total cholesterol is fairly balanced at
5 22.6 percent versus 20 for triamcinolone. There
6 were some more frequent reports of lower HDL, 11.8
7 versus 6 percent for triamcinolone. The LDL
8 cholesterol was fairly balanced. However, there
9 were significant changes in triglycerides, and I
10 would like to highlight that further.

11 But before I do that, I'd like to show
12 clearly that the impact for the cholesterol panel
13 in general is no effect in terms of canakinumab.
14 I've separated the cohorts from phase 2/3 based on
15 their cardiovascular risk factors at baseline.
16 Patients with a cardiovascular risk factor at
17 baseline are on the left, and those without at
18 cardiovascular risk factor at baseline are on the
19 right. And you could see no real clinically
20 significant effect, and if anything, trends in a
21 positive direction in terms of HDL and LDL for
22 canakinumab treatment versus -- or this is just the

1 canakinumab-treated group.

2 Now, as we noted, there are episodes of
3 hypertriglyceridemia that happen during this acute
4 inflammatory condition, and they are more
5 frequently reported and noted for the canakinumab-
6 treated group than the triamcinolone-treated group.
7 We did a thorough evaluation of
8 hypertriglyceridemia in these patients, and we
9 specifically looked for clinical manifestations of
10 hypertriglyceridemia that would impact clinical
11 outcomes, and specifically pancreatitis, and we did
12 not find any evidence based on measure queries of
13 pancreatitis-related terms for pancreatitis in
14 these patients with hypertriglyceridemia.

15 Now, we did look at the rheumatoid arthritis
16 data set for the placebo-controlled data to see if
17 there was any independent hypertriglyceridemia
18 noted with canakinumab use in the rheumatoid
19 arthritis data set. And, again, this is a higher
20 dose. And you can see on this table that the
21 reporting of hypertriglyceridemia was balanced
22 across the canakinumab-treated at 300 milligrams

1 every 2 weeks compared to placebo.

2 Now turning to liver function, you can see
3 the abnormal liver test, or the transaminases ALT
4 and AST, reported across the three doses of
5 canakinumab versus triamcinolone. And you could
6 see for the transaminases in general, there were
7 more frequent AST and ALT abnormalities reported
8 with triamcinolone as compared to canakinumab.

9 There were two cases noted at the bottom row
10 on this table of patients who had an AST and ALT
11 elevation of greater than three times normal in a
12 setting of a greater than 1.5 increase in
13 bilirubin. The first patient, this patient, had
14 abnormal LFTs at baseline, and the end of study lab
15 findings were consistent with their baseline
16 findings.

17 In addition, there was one patient in the
18 150-milligram-treated group, with the two asterisks
19 on this table, and you can see that this patient
20 did have a history of hepatic steatosis. They did
21 have lab abnormalities throughout the study.
22 However, the lab findings at the end of the study

1 were consistent with their baseline values.

2 Now I'd like to turn to uric acid in
3 particular because, clearly, in a gouty arthritis
4 population, uric acid changes can be clinically
5 impactful. What we've shown here is the uric acid
6 changes in patients treated with a single dose of
7 triamcinolone.

8 You can see on the bottom two lines, these
9 are patients on urate-lowering therapy compared to
10 the top two lines, patients who are not on urate-
11 lowering therapy. You can see canakinumab in the
12 blue versus triamcinolone in the yellow. And you
13 can see clearly in the setting of urate-lowering
14 therapy, there is no significant difference in the
15 uric acid levels between the two treated groups.

16 Now, there is a real increase in uric acid
17 that happens in patients not on urate-lowering
18 therapy. This increase is shown very clearly on
19 the top two curves. Canakinumab in the blue does
20 increase. It does increase at the 0.5 milligram
21 per deciliter level. If you do statistics on these
22 changes, you can find that it would be

1 statistically significant. But all of those
2 statistical significant measurements happen in the
3 setting of a 0.5 or 0.6 change in canakinumab
4 compared to triamcinolone. You can also see
5 clearly from this curve that the uric acid levels
6 do return to baseline in this instance, in this
7 population, by day 84.

8 Now, the clear impact of uric acid can be to
9 exacerbate gouty arthritis and result in gouty
10 arthritis flares. We looked very closely at the
11 population in this regard, and what you see on this
12 graph is, on the far left, consider the far left
13 two bars as your baseline bars because they are the
14 flare rate for all patients reporting a serum urate
15 of less than 0.5.

16 Within the gouty arthritis data set, we then
17 made cohorts for the uric acid levels of either
18 greater than 0.5 milligrams per deciliter, greater
19 than 1, or greater than 2, to see if the incidence
20 of flares changed in patients who had hyperuricemia
21 in the setting of canakinumab. And you can see
22 clearly, at all of the reporting cohorts, there's

1 no increase in flare rate in the canakinumab group
2 compared to triamcinolone. And if anything, the
3 efficacy of canakinumab is maintained in these
4 cohorts with hyperuricemia.

5 So although the uric acid levels do change
6 and they do increase, there does not appear to be
7 any clinically adverse consequence in terms of the
8 flare rates in this population on canakinumab.

9 So now I'd like to move to the very
10 critical topic of safety on retreatment. Gouty
11 arthritis is a chronic disease. Patients will need
12 to be retreated, and we need to better understand
13 the safety on retreatment in this gouty arthritis
14 population.

15 In terms of exposure on retreatment, we have
16 118 patients -- you can see on the bottom of the
17 curve, or the bottom of the table -- who've
18 received greater than one treatment of canakinumab.
19 In addition, we have 43 -- or not in addition; a
20 subset of that are 43 patients who've received
21 greater than two treatments.

22 Now, there's a very important reason to

1 understand these numbers because we will see these
2 numbers again in terms of how we measure the safety
3 and how we follow the safety in the retreated
4 population because, clearly, the population can be
5 looked in a pooled fashion versus having the
6 retreated group serve as their own controls.

7 You'll see we have a little bit of a
8 different view on how we monitor for the safety in
9 these two populations because the agency will share
10 some data in terms of looking at the total
11 population and having the populations be compared.
12 The problem with that is some of the comparisons
13 then become confounded by patients who show up in
14 both groups; and also, in addition, in the
15 extensions we have people on triamcinolone who then
16 convert to canakinumab and are retreated with
17 canakinumab.

18 So what we've chosen to do is concentrate on
19 the 43 patients you see on the bottom of this curve
20 because these patients did have more than one
21 treatment, and they serve as their own controls, so
22 we can better understanding on the safety reporting

1 in that population serving as their own controls.

2 You can see on this table the SAEs and AEs
3 in those 43 patients who were looked at before
4 their first retreatment. So the first column on
5 the left is before the first retreatment. So they
6 have their baseline flare. Then they potentially
7 have the period to report adverse events. That's
8 the "Before 1" column on the left, those 43
9 patients. If they have a subsequent flare, they're
10 retreated, and then it's the "After 1" group, the
11 middle column. If they have an additional flare,
12 they're retreated again. That's the "After 2" or
13 the third column.

14 You can see, as expressed here in exposure
15 adjusted per 100 patient years, the incidence of
16 adverse events and serious adverse events, there's
17 no increase in SAEs reported in the before
18 treatment compared to the after first retreatment
19 and after second retreatment. And, importantly,
20 actually, there were no serious adverse events
21 reported in the 43 patients after two retreatments.

22 Similarly, you can see the exposure-adjusted

1 reporting numbers for the adverse events, 547, 376,
2 and 378. So no increase in event reporting. And
3 I've listed the system organ classes for your
4 information in the remainder of the table. So,
5 clearly, by this data set -- and it is
6 43 patients -- the retreatment does not lead to an
7 increase in AEs or SAEs.

8 Now, we have also supplied information at
9 the preferred term level so you can get just a
10 deeper understanding of the retreatment safety in
11 this critical safety population. It's also
12 important to note on this slide that this is
13 adjusted per hundred patient years, and the
14 number -- actually, each 4 represents one event.
15 So where you see 24, that would be 6 events; where
16 you see 8, that would be 2 events. So there are
17 relatively few events, but no real significant
18 increased reporting across the retreated
19 population.

20 So now I'd like to move to a summary and as
21 I'm safety recommendations. What we've shown here
22 is the overall safety profile is consistent with

1 the postmarketing experience we've seen with CAPS
2 and the mechanism of action for this anti-
3 inflammatory therapy. In this patient population,
4 with the high incidence of comorbidities, reported
5 deaths were consistent with the underlying medical
6 conditions, and major adverse cardiac events were
7 balanced across treatment groups, and blood
8 pressure changes were not clinically significant.

9 In terms of lipid metabolism, there were no
10 significant changes in cholesterol, either HDL or
11 LDL, and triglyceride changes were apparent and did
12 occur; however, these changes were not linked to
13 adverse clinical consequences, and in our case, a
14 very deep review of pancreatitis.

15 There were no confirmed cases of treatment-
16 related renal failure, and changes in renal
17 function were transient and reversible. And with
18 long-term exposure greater than tenfold estimated
19 in the gouty arthritis population, which we would
20 calculate at potentially three injections over a
21 year, there was no effect on renal function.

22 In terms of uric acid, there is an increase

1 in uric acid levels. This does return to baseline,
2 and there is a uric acid level decrease with
3 concomitant urate-lowering therapy. It's important
4 to note that the increase in uric acid levels is
5 more evident in patients not on urate-lowering
6 therapy, which is a standard of care within gouty
7 arthritis populations. However, this increase in
8 uric acid does not portend an increase in gouty
9 arthritis attacks.

10 Anti-canakinumab antibodies were found in
11 approximately 1 percent of treated patients, and no
12 immunogenicity adverse events were reported in this
13 limited data set.

14 Neutrophil decreases were transient and
15 reversible, and none were less than the very
16 clinically relevant threshold of less than 500 per
17 10 to the ninth liter, per liter, in the
18 150-milligram group.

19 It is important to note, and healthcare
20 providers need to be reminded, and it's currently
21 in our labeling for the CAPS population as a
22 warning and precaution, that canakinumab is

1 associated with an increased risk of infections.
2 Serious infections temporally related to decreased
3 neutrophil counts have been reported, and these
4 importantly have responded to standard of care.
5 And no opportunistic infections were observed.

6 So in terms of ensuring patient safety post-
7 approval, we would pursue aggressive opportunities
8 to identify the appropriate patient population.
9 Clearly, as was alluded to earlier by Dr. Mundel,
10 we're looking at a very targeted patient
11 population, roughly 6 percent of the gouty
12 arthritis population or 300,000 patients.

13 Our orphan status indication in CAPS
14 resulted from that population being less than
15 200,000 patients. So this population, we're
16 looking at maybe 300,000, so 100,000 more than may
17 be classified as an orphan indication. But clearly
18 these actual and potential risks need to be
19 communicated to physicians, and we need to take
20 every opportunity to help healthcare providers use
21 the drug appropriately in the appropriate
22 population.

1 In addition, we would pursue
2 pharmacovigilance, routine pharmacovigilance,
3 including our cumulative safety evaluations.
4 However, targeted follow-ups of serious clinical
5 trial and postmarketing cases could be pursued.
6 Targeted questionnaires or checklists in key areas
7 specifically looking at infection or malignancy or
8 hypersensitivity could be pursued.

9 In addition, we do have adjudication
10 committees that go on regularly, and we do have
11 them as a part of our gouty arthritis problem. I
12 mentioned it for CV. We also have that for
13 malignancies, and we also have that for infections.
14 And we do thoroughly review these important cases
15 in our clinical development programs.

16 Finally, we could propose a registry to
17 further evaluate the risk over the long term. We
18 recognize chronic gouty arthritis as a long-term
19 disease. We could certainly pursue a registry that
20 could include up to 3,000 patients and follow them
21 for up to a year or so. But in addition, we do
22 currently have a cardiovascular study that

1 Dr. Mundel mentioned earlier that's ongoing and
2 will include 7,200 patients. This is a very large
3 patient population.

4 These patients are at high cardiovascular
5 risk. They will receive 150 milligrams of
6 canakinumab every quarter, every 12 weeks, and the
7 study will run for approximately 3 to 4 years. And
8 this study is actively monitored by our data safety
9 monitoring board. So we would have that running in
10 parallel. That study has actually started, and
11 we've had enrollment in that, and that happened,
12 and the study kicked off in April.

13 So with that, I'd like to conclude the
14 safety presentation and turn it over to
15 Dr. Wortmann for clinical perspectives.

16 **Sponsor Presentation - Robert Wortmann**

17 DR. WORTMANN: Good morning. I recently
18 became a consultant for Novartis, and they have
19 paid for my transportation to this meeting. And
20 part of what they asked me to do was to review the
21 data that has just been shared with you to give my
22 perspective on it as a physician who's been

1 interested in studying gout for over 35 years.
2 And, frankly, after reviewing it, I'm quite
3 excited. I think this is very, very exciting data.

4 I want to agree with Dr. Edwards that there
5 is an unmet need for a certain subpopulation of
6 patients with gout. And I just want to share this
7 patient. I was asked to see this patient about two
8 months ago, and the picture of her finger, I think,
9 tells you more than a thousand words could about
10 how debilitating and painful this disease can be.

11 That's a tophus, for those of you who aren't
12 familiar with what gout is. It's a solid
13 accumulation of uric acid crystals. It's
14 surrounded by a mantle of inflammatory cells. It's
15 eroding the skin, the bones, the cartilage. It's a
16 very destructive lesion.

17 This woman had been having one attack of
18 gout per month for the last year, and these attacks
19 weren't four or five days; they were lasting almost
20 a month each. She was just miserable. She had
21 comorbidities, and many gout patients have, of
22 hypertension, congestive heart failure. She was an

1 insulin-dependent diabetic. She had chronic renal
2 failure. And so, obviously, for those of you who
3 know the contraindications and problems we have
4 with colchicine and nonsteroidal anti-inflammatory
5 drugs or corticosteroids, these weren't great
6 choices for this woman.

7 So there is an unmet need, and the need is
8 for a therapy for gout patients in whom existing
9 therapies are ineffective, cannot be tolerated, or
10 are contraindicated. Fortunately, it's a small
11 group of people, but it's a real group of people.

12 This data I've chosen to show you -- because
13 it's taken to look at the reduction of pain in
14 patients who were treated in the first 24 hours of
15 their gout attack as opposed to the pooled data.
16 And this was the result of the percentage of
17 patients who improved on the vertical axis versus
18 the percent improvement on the horizontal axis at
19 6 hours, at 12 hours, at 24 hours -- you can really
20 see the blue line, which is canakinumab, separating
21 from triamcinolone -- at 48 hours, and then at
22 72 hours. And this showed that over 90 percent of

1 the patients had moderate response, and over
2 50 percent had had substantial response to
3 canakinumab.

4 This translates into being able to have a
5 conversation because you're not distracted by this
6 terrible pain. Being able to put a shoe back on.
7 Going back to work. This response indicates a
8 great improvement in quality of life.

9 This is an anti-inflammatory agent. This
10 shows four of the traditional parameters of
11 inflammation and how canakinumab affected them
12 compared to triamcinolone. At the end of 72 hours,
13 72 percent of the patients had no pain; 40 had no
14 tenderness; 42 had no swelling; and 76 had no
15 erythema; so a potent anti-inflammatory.

16 What's really impressive also to me is that
17 it was sustained. Seventy-two percent of the
18 patients who received 150 milligrams of canakinumab
19 were pain-free at six months. Seventy-two percent
20 went six months without having a recurrence. Now,
21 remember, the people who came into these studies
22 were averaging six to seven flares a year. That's

1 a lot of morbidity. To eliminate that is very
2 significant for these people, and cost-effective,
3 probably because of the long half-life, the 26
4 days. This anti-inflammatory effect is prolonged
5 with this drug compared to other agents we use, and
6 that's probably why they have less flares.

7 So, overall, 80 percent of patients had a
8 major clinical benefit from this drug, defined as
9 major pain relief and no recurrent attacks, which
10 is up to 65 percent at 24 weeks; or a consistent
11 benefit, meaning they got better, then they flared,
12 and then they got better again.

13 Now, there are risks to all medicines, and
14 including this one, and one of them that we would
15 be very concerned about is infection. The data was
16 reviewed. And, fortunately, the serious infectious
17 events were small in number. They were managed
18 with the usual treatments for these conditions.

19 We actually can predict that infection would
20 be something we'd be concerned about based on the
21 mechanism of action of the drug, and it inhibits
22 interleukin-1. That's one of the things we'd be

1 worried about. But the risk turned out to be
2 pretty low.

3 You've seen the data on the decreased
4 neutrophils, and most of the decreases were small
5 and values remained within normal limits. And
6 there was no correlation with the decreases in
7 infections. But I'd like to -- as a clinician, I
8 want to remind you that when people have gout
9 attack, we think about their toe being inflamed or
10 their knee being inflamed. But their whole body's
11 got inflammation. Their sed rates go up. Their
12 CRPs go up. Their white blood counts go up. They
13 can get fever.

14 So if you measure your first white count
15 when a person's having an attack, it's likely going
16 to be higher than at the time of their baseline.
17 As the inflammatory response resolves with
18 treatment, the white count's going to fall. So I
19 think that's a good part of why we saw that
20 decrease, and then it came back to normal.

21 Two other laboratory values that we want to
22 address are the triglyceride changes. The

1 increases were small. I think the average was
2 about 20 milligrams per deciliter. There was no
3 evidence they were harmful. And I don't know if
4 there's even a benefit to lowering the triglyceride
5 by 20 millimeters [sic] per deciliter.

6 The uric acid changes were small, averaged
7 at .5 milligrams per deciliter. And this again,
8 like with the white count going down with
9 treatment, it's likely with treatment of a gout
10 attack, your uric acid will go up. And the reason
11 for that is when we get this inflammatory cascade
12 that is primarily triggered by IL-1, one of the
13 other cytokines that is released is IL-6. IL-6 is
14 uricosuric.

15 So it is usual, when a person gets an
16 attack, for their uric acid to go down a little
17 bit; when it's treated, that IL-6 disappears, uric
18 acid excretion that is increased is now not
19 decreased, and so the uric acid will go up. In
20 fact, 30 percent of people with acute gout attacks
21 can have normal uric acids during the attack
22 because of this factor. And also, the observed

1 increases did not seem to associate with any
2 increased attacks.

3 So I think canakinumab is the first and only
4 targeted anti-inflammatory agent to potentially be
5 available for the treatment of gouty arthritis.
6 The PK profile of this drug renders it an effective
7 agent for rapid relief of acute attacks, but it has
8 a durable response because of its prolonged half-
9 life. It provides a very effective option for an
10 appropriate subset of patients with gout, and I
11 think it has a manageable safety profile for this
12 generally sick and complicated population.

13 I'd like to go back to this slide that
14 Dr. Edwards showed you, the natural history of
15 gout, and emphasize a point about the
16 pathophysiology of this disease. This disease
17 develops in people who are hyperuricemic, and it
18 develops because their hyperuricemia, their body
19 fluids have uric acid. They're super-saturated
20 with uric acid, so crystals can form.

21 When crystals form and the person remains
22 hyperuricemic, more crystals form on top of that.

1 They aggregate. We call aggregates of uric acid
2 tophi. So all gout is tophaceous, and the tophi
3 are starting to form early on in the disease.

4 As the disease progresses, these tophi get
5 bigger. And finally, during the end stage of the
6 disease, we can see them and feel them. Those
7 tophi are surrounded by a mantle of inflammatory
8 cells, and histochemically, IL-1 is in that mantle.
9 So this disease is destructive even when it's not
10 causing this intense inflammatory response.
11 Canakinumab has a place for this end of the
12 spectrum of this disease.

13 So I started with this picture of this
14 finger. Two days after this picture was taken,
15 this finger was amputated and this woman was
16 delighted with the result. She no longer had the
17 burden of this chronic, severe, debilitating pain.
18 I want this drug to use by patients so they don't
19 have to go through this.

20 Thank you.

21 DR. O'NEIL: Thank you. And I'd like to
22 begin by thanking the sponsors for keeping to time.

1 It's rather novel, in my experience chairing this
2 committee.

3 [Laughter.]

4 **Clarifying Questions for the Sponsor**

5 DR. O'NEIL: I would now like to -- we now
6 proceed to discussion of the data presented by the
7 sponsor. And this will be limited to clarifying
8 questions for the sponsor. I would like to open
9 this up to the panel and ask you to remember to
10 state your name before you speak, and when you are
11 done speaking, please turn off your microphone.

12 All right. The first question will be from
13 Dr. Gibofsky.

14 DR. GIBOFSKY: My question is I think for
15 Dr. Wortmann.

16 Bob, I share your enthusiasm about the data,
17 and I share your and Larry's concerns about the
18 unmet needs. I just wonder if the risk/benefit
19 equation couldn't have been met with a lower dose
20 of the drug, particularly because I believe we
21 heard from Dr. Mundel in his opening remarks that
22 the agency did not require demonstrating

1 superiority to triamcinolone in the protocol
2 assessment. And, thus, I wonder about the
3 selection of the 150-milligram dose as opposed to
4 something lower than that.

5 DR. WORTMANN: I don't really think I'm the
6 one to answer that question. I've only seen the
7 data. I didn't have anything to do with the design
8 of the trial. And I'm convinced that the
9 150-milligram dose is very effective, and the
10 action of it is sustained. And I think the risk is
11 very low compared to -- for this sick population.

12 DR. GIBOFSKY: Would it have been lower at a
13 lower dose? Could we achieve the same
14 risk/benefit, which I think we need, at a lower
15 dose of drug, particularly if a higher dose or
16 superiority to triamcinolone was not required by
17 the agency.

18 DR. WORTMANN: I'm going to let Marjorie
19 talk about that.

20 DR. GATLIN: Thank you. So the data from
21 our phase 2 dose-ranging trial clearly demonstrates
22 that 150 offered the optimum effect in terms of

1 rapid and effective pain relief in this very
2 painful disease.

3 If I could have the slide up. Just remind
4 the committee, this is our data from our phase 2
5 trial, where we showed that there was rapid and
6 sustained pain relief with the 150-milligram dose
7 that was not achieved with a lower dose. And if I
8 could have slide E-14, please, I would like to show
9 that we assessed other parameters with regard to
10 the relative benefits of the 150-milligram dose to
11 the 90-milligram dose.

12 So if we could focus on this column here,
13 which shows the results of the 150-milligram dose.
14 I'm going to walk you through a number of
15 parameters that show that 150 provided the optimal
16 pain benefit for these patients, where you want to
17 get in on top of the pain and reduce their pain
18 very quickly.

19 So when one looks at the patient and
20 physician assessment of response, it was
21 significantly better with the 150 compared to lower
22 doses. When one looks at the use of rescue

1 medication, only six patients required rescue
2 medication, and only two of those took an oral
3 steroid. And, again, the safety seen in the
4 program was flat across all the lower doses.

5 So I believe we've clearly demonstrated that
6 the 150-milligram dose is the dose that provides
7 the optimal pain relief in this setting and is an
8 acceptable safety profile.

9 DR. O'NEIL: And that was Dr. Gatlin, for
10 the record.

11 DR. EDWARDS: And this is Dr. Edwards, and
12 I'd like to comment to Allan's statement.

13 I think all of us that treat a lot of gout
14 are generally disappointed in the rapidity of
15 relief of pain that our current drugs offer us,
16 whether that's colchicine, nonsteroidals, or even
17 steroids. I think something that gets to the point
18 quicker and reduces the pain faster is always a
19 better dose, provided you're not going to be
20 overweighed by toxicity in that particular setting.

21 You should also remember that this decrease
22 in pain equates to better multifunctional scales,

1 and so Dr. Strand has reviewed that for this. And
2 so in real terms, this is being able to get up out
3 of bed days earlier. This is being able to put on
4 your shoes days earlier. This is being able to get
5 back to work days earlier, just from the kind of
6 difference that Dr. Gatlin's data showed you.

7 So I think putting it in functional terms, a
8 small change on that graph going horizontally makes
9 a big difference over daytime.

10 DR. STRAND: I'm Vibeke Strand. I'm a
11 clinical professor in the Division of Immunology
12 and Rheumatology at Stanford. And I just wanted to
13 briefly show you some data with the patient-
14 reported outcomes, secondary outcomes.

15 Basically, they were not statistically
16 different from triamcinolone as we might expect
17 because, for instance, with the health-related
18 quality of life -- SF-36, slide up -- it was
19 actually assayed first time at baseline and then at
20 one month, and subsequently at 8 and 12 weeks. So
21 I'm going to show you, just for understanding, the
22 significant benefit that patients reported with

1 this treatment.

2 If you look at the top of the graph, that's
3 the physical function domain of the SF-36; role
4 physical, bodily pain, and general health
5 perceptions are going clockwise. Vitality, meaning
6 fatigue and pep and energy, is at 6:00; social
7 function, role emotional, mental health. The
8 scores go from 0 to 90. The grid marks are
9 10 points each. And that represents two times the
10 minimum clinically important difference.

11 Next, please. We can see here are the
12 baseline scores, and this is in the U.S. phase 3 or
13 North American phase 3 study. And if you go next,
14 please, you can see the age- and gender-matched
15 U.S. normative population's match for this
16 protocol. One looks at physical function, role
17 physical, and bodily pain, are very significantly
18 impacted by the acute gout at baseline, but so are
19 the other domains.

20 Next. The improvement at 30 days now
21 actually normalizes the scores in five of these
22 domains. These are some of the largest

1 improvements I've seen in an SF-36, and
2 with -- next, please -- 8 weeks and 12 weeks of
3 treatment, one has some continued benefit. So this
4 benefit is sustained.

5 Very quickly, just to show you the
6 comparison to triamcinolone, we have similar
7 baseline impact and now improvement at 4 weeks, and
8 at 8 and 12. This is a little bit of slower
9 improvement, but significant as well, and does
10 indicate that the triamcinolone dose was effective.

11 DR. O'NEIL: The next question is from
12 Dr. Buckley.

13 DR. BUCKLEY: I think I agree with all the
14 people who've spoken so far that there clearly is a
15 need for alternative medications for acute gout
16 attacks, especially ones that will work fairly
17 quickly. The population of patients it seems most
18 difficult to treat are patients with renal
19 impairment because we're so limited in our ability
20 to use nonsteroidals and colchicine, and to some
21 extent even glucocorticoids because of fluid
22 retention issues.

1 The data that Dr. Edwards presented said
2 when you look at a gout population overall, you
3 have about 47 percent renal impairment. And the
4 patient that Dr. Wortmann presented is an
5 interesting patient, and I've had one like her this
6 year. She has terrible gout but significant renal
7 impairment.

8 So I'm trying to understand these data and
9 risks and benefits for those types of patients.
10 But in this study -- I think in one study there was
11 10 percent with renal impairment, 15 percent in the
12 other, and an exclusion was severe renal
13 impairment.

14 So I have a couple of questions. One is
15 some simple definitions; what was the definition of
16 severe renal impairment? The second was why did
17 they exclude it? Because that's the population we
18 really need to know about. When I look through the
19 data, it doesn't look like the drug changes -- that
20 the elimination of the drug is dependent on renal
21 function.

22 So why were those patients excluded? Since

1 they were excluded, what data do we have about
2 efficacy, but probably more importantly, adverse
3 events in that population of 10 to 15 percent who
4 had renal impairment?

5 We know people with renal impairment are not
6 just at risk for worsening of their kidney function
7 but are at much more risk for infection and
8 cardiovascular disease. So in that high-risk
9 population, the population I think we need to know
10 most about, do we have any data about serious
11 adverse events?

12 DR. GATLIN: Gatlin, Novartis. I heard two
13 questions there about the efficacy in patients with
14 renal impairment, our exposure in patients with
15 renal impairment, a question about why did we
16 exclude those patients, and then a question about
17 safety.

18 So first I'm going to speak to the question
19 about exclusion. We excluded patients with severe
20 renal impairment, defined as a creatinine clearance
21 of less than 30 mLs per minute, and that was in
22 taking a conservative approach in this clinical

1 trial program.

2 If I could have the slide up.

3 We did enroll a number of patients with
4 varying degrees of renal impairment. At the top of
5 this slide, you can see the numbers that I showed
6 you with regard to comorbidities in terms of
7 14.7 percent of patients with chronic kidney
8 disease reported as a comorbidity. However, when
9 we -- and we do have efficacy data on that
10 population, which I can share with you.

11 But we also had a number of patients with
12 some degree of renal dysfunction at baseline
13 measured at GFR. Approximately 30 percent of the
14 patients had a GFR below 60, and another
15 significant proportion of the patients, about half,
16 had renal impairment defined as GFR below 90. In
17 fact, there was no pharmacokinetic differences
18 observed for canakinumab regardless of renal
19 function.

20 If I could have the slide up. When we look
21 at that, 15 percent of patients who had a CKD
22 reported as a comorbidity at baseline, there was a

1 similar pattern of efficacy with regard to pain
2 relief compared to the steroid comparator as to the
3 overall population. And if I could have the slide
4 up, please. There was also a significant benefit
5 in terms of reducing the risk of the next gouty
6 arthritis attack in that population.

7 DR. CHARNEY: Hello. I'm Dr. Alan Charney.
8 I am a medical director at Novartis and a professor
9 of medicine at New York University, where I was
10 former chief of the nephrology section at the VA.
11 I'd like to comment right now, if I might, on the
12 effects on renal function by canakinumab, if I
13 might. And I'd like to show first, if I might,
14 slide 83.

15 Here we see on the top part of this slide
16 that there were changes in GFR in the course of the
17 trial, and these were recorded as single events, as
18 they were. But if we look at the bottom part of
19 this slide, we see that sustained changes,
20 sustained reductions in GFR, were only observed in
21 about 1 percent of patients.

22 So what we see in the top part of this slide

1 is that GFR is variable. And variability in GFR is
2 very common both in normal patients and
3 particularly in patients who have CKD. And the
4 average GFR in this group of patients with gouty
5 arthritis was approximately 70 mLs per minute,
6 which is, of course, stage 2 CKD. So it's not
7 surprising that we have this kind of variability.

8 A better way to look at the effects of
9 canakinumab on GFR is to look at the next
10 slide -- slide up, please -- and this slide shows
11 the mean GFRs at the initiation of the gouty
12 arthritis subset of patients. And you can see here
13 that the average GFR was approximately 70 mLs a
14 minute. And although there was some variability in
15 the course of the trial, by six months time there
16 were minimal changes in GFR.

17 These were obviously not clinically
18 significant, and I should mention just for the
19 record that the variability in GFR during the
20 course of a trial and during the course of patients
21 with CKD is not known to have any clinical
22 significance. That's a very important point.

1 I think we can look as well at -- slide up,
2 please -- this slide. These are
3 patients -- looking at the numbers of AEs in
4 patients with various levels of GFR, down into
5 the -- we have stage 2, stage 3 in the middle, and
6 stage 4 at the bottom area. And you can see very
7 clearly that there's no increase in AEs or SAEs in
8 the canakinumab group as compared to the
9 triamcinolone group. So that's a very important
10 finding.

11 Finally, I want to say that -- if I could
12 have slide 84, please. I'd like to show a slide
13 that was shown once previously, which shows that in
14 patients with CKD in particular, that canakinumab
15 had no negative, no detrimental effect on the GFR
16 in these patients during six months of therapy.
17 And moreover, there was a reduction in
18 microalbuminuria in these patients. This is not a
19 small thing. This is a very important factor.

20 If we look long-term now -- and that, we
21 would have to look at the rheumatoid arthritis
22 cohort of patients, and that would be slide S207.

1 Slide up, please. Here we followed
2 GFR -- if we look at the bottom part of this
3 slide -- over a period of almost three years. And
4 to remind everyone, these patients were treated
5 with more than tenfold increases in exposure to
6 canakinumab as compared to the gouty arthritis
7 patients.

8 As you can see -- let me use the pointer
9 here -- look at the mean change in GFR here. And
10 you'll see that over the course of this treatment
11 period, over 144 weeks, we have reductions in GFR
12 ranging from about 3 to about 8 mLs per minute over
13 a course of about three years.

14 Now, this reduction in GFR is entirely
15 expected in a patient population with stage 2 CKD
16 that loses GFR ordinarily at the rate of between 2
17 and 4 mLs per minute per year. As you know in
18 normal patients, we all begin to lose GFR at around
19 age 40, in the range of 1 to 2 mLs per minute per
20 year. And patients with CKD lose it at about
21 double that rate.

22 So this rate of reduction in GFR in these

1 patients is entirely consistent with a progressive
2 loss of GFR independent -- independent -- unrelated
3 to canakinumab therapy.

4 Thank you. Slide down, please.

5 DR. BUCKLEY: So, in summary, I think what
6 I'm hearing was that patients with more serious
7 renal disease were not enrolled, not because they
8 couldn't be -- this drug wouldn't work -- but
9 because the decision was made to be conservative.
10 But, again, it leaves us with a dilemma that we
11 don't have information on the patients that we
12 might need to have most information on.

13 It did appear, when you looked at the
14 serious adverse events, that they were going up.
15 And you didn't separate them by infection, which is
16 I think the one we worry about most. But they were
17 going up as renal failure was going down, or renal
18 function was going down. So still I guess I'm left
19 with some concerns.

20 DR. SHETZLINE: Mike Shetzline, program
21 head. No, it is true. In our protocol, we didn't
22 study the most severe cases of renal dysfunction.

1 That is true; Stage 5.

2 DR. O'NEIL: The next question is from
3 Dr. Mikuls.

4 DR. MIKULS: I'd like the sponsor to help me
5 understand how you envision this drug being used.
6 And so I guess what my question is specifically
7 getting at is you envision this as an on-demand
8 drug that's repeated at a specified interval. I
9 ask that question in light of you focusing on only
10 43 patients with repeat dosing. Big issue in my
11 mind.

12 I have a second question, and my second
13 question is, you presented very nice data that
14 those who respond the first time are likely to
15 respond the second time, which suggests a
16 durability of response. Very nice. But the coin
17 flips the other way. So it also seems to be that
18 those who don't respond the first time don't
19 respond the second time. So it doesn't make sense
20 for that patient, who doesn't respond the first
21 time, to be getting the drug a second, a third, a
22 fourth, a fifth time.

1 DR. SHETZLINE: Yes. So in terms of how we
2 envision the drug being used, the drug is currently
3 labeled for CAPS, to be administered every 8 weeks.
4 We envision, obviously, in our study population,
5 and as Dr. Gatlin highlighted, there were only
6 about 15 percent of patients who re-flared in the
7 first 12 weeks, and an additional 15 in the next 12
8 weeks, so 6 months.

9 So as an on-demand therapy, clearly there
10 would be very infrequent dosing on a yearly basis
11 in the vast majority of populations. But we do
12 envision it being a flare-based on-demand therapy
13 for gouty arthritis sufferers.

14 In terms of the reproducibility of the
15 efficacy, I'll let Dr. Gatlin address that.

16 DR. GATLIN: Gatlin, Novartis. So if I
17 could have the slide up, please. Yes, the efficacy
18 of canakinumab is reproducible from the baseline
19 attack to subsequent attacks. I'd like to point
20 out that this panel on the left, in terms of the
21 reproducibility and efficacy, it's not just the
22 second attack; it is the last post-baseline attack.

1 So even in patients that had more than one
2 subsequent attack, that efficacy was maintained,
3 albeit that wasn't a small number. But this is
4 substantial repeat efficacy in the last post-
5 baseline attack, and it is clear that we believe
6 this could be important guidance for physicians,
7 that if a patient does not respond to that initial
8 treatment, there does not seem to be a rationale
9 for repeat dosing of those patients.

10 DR. MIKULS: And that will be reflected in
11 your proposed labeling?

12 DR. GATLIN: Well, it certainly would be
13 described as a factor. And what's actually in the
14 labeling I would leave to one of my regulatory
15 colleagues to describe. But certainly we believe
16 that that is information that physicians should be
17 aware of and should consider.

18 DR. O'NEIL: Next question is from
19 Dr. Felson.

20 DR. FELSON: So I wanted to ask you about
21 the claim language and evidence supporting it
22 because I didn't see any evidence in the sponsor's

1 presentation on the last phrase, "and reduce the
2 frequency of subsequent attacks," which actually
3 gets a lot at what Dr. Mikuls just asked.

4 Can you comment on where evidence supports
5 that, please?

6 DR. GATLIN: Yes, I can. We have
7 demonstrated -- if I could have the core slide with
8 the number of attacks. We have clearly
9 demonstrated in our program that canakinumab not
10 only reduces the risk of subsequent attacks, but
11 reduces the number of mean attacks per patient, and
12 reduces the risk or reduces the total number of
13 attacks that patients have.

14 We'll pull up the slide from the core
15 presentation that shows that. But what we did
16 show, while we're finding the slide, is that the
17 mean number of attacks per patient -- slide
18 up -- the mean number of attacks per patient, and
19 this is through 24 weeks, was less than half that
20 seen with triamcinolone.

21 DR. FELSON: That's not a mean number of
22 attacks per patient. That's a hazard ratio of the

1 initial attack. That does not speak -- based on
2 the analytic plans provided, that's a Cox
3 proportional hazards model result, and that's time
4 to event for the first attack. That speaks not at
5 all to the subsequent attack frequency. And
6 there's no statistical test that you've presented,
7 to my knowledge, that speaks to the subsequent
8 attack frequency.

9 Is that correct?

10 DR. GATLIN: I'm going to turn that over too
11 my statistician to answer your question.

12 DR. GALLO: Paul Gallo, Novartis statistical
13 methodology.

14 Slide up. This is a different slice of the
15 same data you just looked at.

16 DR. FELSON: So can you answer my question
17 first, please?

18 DR. GALLO: Yes. Sure.

19 DR. FELSON: Does the data just presented
20 speak at all to the risk of subsequent attack?

21 DR. GALLO: I believe the data speaks to the
22 risk of the subsequent attack.

1 DR. FELSON: The data you have presented now
2 as opposed to the data you presented during the
3 last slide?

4 DR. GALLO: I believe this slide does, and I
5 have an additional slide that does.

6 DR. FELSON: All right.

7 DR. GALLO: So basically here we're counting
8 patients with multiple attacks. So, for example,
9 in the 6-month data, there are 20 patients in the
10 triamcinolone group that have at least three
11 attacks, and only three in the triamcinolone group.

12 We can do a statistical test of time from
13 randomization to second flare or to third flare in
14 addition to first. Those hazard ratios on the
15 bottom are highly significant. We did actually do
16 a statistical analysis, a more complex one, of time
17 to multiple flares. It pretty much tells the same
18 story.

19 So at least through six months, the effect
20 as seen in time to first flare does hold up through
21 time to second and third flare. I can't really say
22 more than that because we don't see many patients

1 flaring four times, none in the canakinumab
2 treatment arms.

3 DR. FELSON: You were going to show another
4 slide yet?

5 DR. GALLO: Okay. ST-45. Slide up.

6 This is kind of getting a little bit deeper
7 into statistics. This is an intensity curve from
8 an analysis that analyzes multiple flares. So,
9 basically, this extends the Kaplan-Meier curve that
10 basically says what's the chance that a patient
11 will have a flare by a certain time.

12 This is factoring in multiples. So what's
13 on the Y axis is really the expected number of
14 flares per patient by any given point. The hazard
15 ratio from multiple flares across the whole six
16 months is .42, which is even a little bit lower
17 than the hazard ratio for time to first flare,
18 which is .44.

19 Another interpretation of this graph is that
20 if efficacy was being lost, we would expect that
21 blue line there not to stay straight but to start
22 to curve up if towards the end of this period flare

1 efficacy was being lost.

2 DR. O'NEIL: Thank you.

3 We're running very short on time.

4 Is this a crucial response?

5 DR. KOCH: Yes. I think it could be. If we
6 could go back to the slide 57 from the core
7 presentation. And I'm Gary Koch, biostatistics
8 department, University of North Carolina. And I
9 have activities on behalf of Novartis through an
10 agreement with my university. So slide up.

11 So my understanding is that this is actually
12 addressing the distribution of the number of
13 attacks a patient had, as shown in the bottom half
14 of the slide. And it is addressing that through
15 what would be the mean of those distributions.

16 So then the analysis that is being displayed
17 here is addressing the count for the number of
18 attacks, using a negative binomial regression
19 model, and it then estimates what would be the
20 ratio of those means. And so that's what's shown
21 in the second line. And then the confidence
22 interval and p value do pertain to that.

1 So this particular display is indeed
2 addressing a comparison of the arms for the
3 distribution of number of attacks through the count
4 of those number of attacks and a statistical model
5 for those counts.

6 DR. O'NEIL: Thank you.

7 We will take two more questions from the
8 panel, and there will be time for further
9 discussion later.

10 Ms. Aronson, please.

11 MS. ARONSON: I have a three-part question.
12 The first is just a question about the practical
13 side of qualifying to take the drug. Should this
14 be approved, the sentence that would be most
15 appealing to a patient consumer is probably,
16 "extend the time to next attack and reduce the
17 frequency of subsequent attacks." So I want to ask
18 about that.

19 It also references several times in the
20 materials that we were asked to review that the
21 drug has to be given early. So if I'm a patient
22 that shows up to a new physician and says, I'm

1 really interested in having fewer attacks, how
2 practically can you define "early"? I did see once
3 a reference to five days. But how is that serious
4 patient identified so that this is an appropriate
5 patient to get the drug?

6 The second part is the demand dosing, a
7 question that it's allowed in 14 days. And I have
8 a question about the half-life being 25.6 days and
9 how that impacts comorbidity.

10 The third part is, you referenced in the
11 presentation early on today this phase 3 for JRA.
12 But did I read somewhere that the rheumatoid
13 arthritis trial was halted? Could that be
14 clarified? And if so, I'm curious about that
15 because those patients were getting the drug more
16 frequently.

17 DR. SHETZLINE: In terms of your question in
18 terms of the rheumatoid arthritis program, the
19 rheumatoid arthritis program was stopped due to
20 what the company perceived as insufficient
21 efficacy. The study did have efficacy compared to
22 the comparator, but given the other rheumatoid

1 arthritis products available on the market, it was
2 not felt that that was to be competitive. And,
3 actually, that data is published, and it's in the
4 public domain, the results of our rheumatoid
5 arthritis program.

6 You had an additional question?

7 DR. GATLIN: So just to clarify, I
8 understood you had a question about how patients
9 would get the therapy because it's on demand.

10 MS. ARONSON: I'm sorry. That part was the
11 question about the 14 days for retreatment and
12 considering the half-life and the comorbidity
13 issues.

14 DR. GATLIN: Okay. So I will address the
15 question with regard to how patients will get the
16 product, and I'd like Dr. Edwards to provide his
17 clinical perspective, and then perhaps I could have
18 another colleague address the issue of the
19 pharmacokinetics.

20 So this is an on-demand product that will be
21 healthcare provider-administered. Given our target
22 patient population in terms of patients who are

1 unable to get adequate response to NSAIDs and
2 colchicine, this is not foreseen as a treatment for
3 your newly diagnosed gout patient. The patient
4 will have to see the physician.

5 We would encourage physicians to identify
6 these patients in their practice and get them
7 prepared, during the intercritical period such that
8 when they do have their next gouty arthritis
9 attack, they will be available -- able to avail
10 themselves of the therapy as early as possible in
11 the onset of that attack.

12 DR. EDWARDS: Edwards. In response to your
13 question, all treatments for acute gout should be
14 initiated as early in the course of the acute event
15 as possible. They're most effective in that
16 regard, whether it's nonsteroidals, colchicine, or
17 even steroids. Once this inflammatory cascade has
18 resulted in the drawing in of more and more white
19 cells and the release of more and more cytokines,
20 it becomes very difficult to treat.

21 Patients in this study were enrolled
22 anywhere from 1 to 5 days after the initiation of

1 the therapy, and I was quite impressed that even
2 those that were enrolled later from the initiation
3 of the pain did respond very nicely. That's
4 something that we don't see across the board with
5 the other forms of nonsteroidals and colchicine.

6 DR. O'NEIL: Thank you.

7 DR. SHETZLINE: I think she had an
8 additional question on the 14 days versus the half-
9 life of canakinumab.

10 So we did the clinical trial with a 14-day
11 interval strictly to address the patients' needs in
12 terms of a gouty flare that may last 7 to 14 days,
13 and they would have the opportunity if they had a
14 subsequent flare to get the canakinumab again. It
15 was really based on the safety data we had, and I
16 showed it through some of my presentation, that we
17 had safety data at the every-2-week interval to
18 support a safe use of the drug at that interval.
19 So the trial was designed that way.

20 Necessarily now going forward, given the
21 half-life, given the efficacy, and the data we
22 have, we're not necessarily saying what the

1 interval needs to be because it's on-demand
2 therapy. But our current labeling is every 8 weeks
3 in CAPS.

4 I think you also had a question about the
5 juvenile arthritis program.

6 Oh, no? Okay. So thank you.

7 DR. O'NEIL: Dr. Suarez-Alvarez is the
8 last -- Almazor, sorry -- will ask the last
9 question.

10 DR. SUAREZ-ALMAZOR: Yes. I would like to
11 have a little bit more clarification about the
12 indication. The case that Dr. Wortmann presented
13 is a patient who cannot take NSAIDs, colchicine, or
14 corticosteroids; however, the approval is being
15 sought for patients who cannot tolerate colchicine
16 or corticosteroids. Therefore, it's being proposed
17 as an alternative to corticosteroids -- sorry,
18 colchicine or NSAIDs. That's what it's being
19 sought for.

20 I'd like to understand what the clinical
21 rationale for that might be and whether this would
22 not be the best drug that can be used as a step-up

1 strategy for those patients who show no response to
2 corticosteroids in previous flares, as opposed to
3 an alternative to corticosteroids.

4 DR. SHETZLINE: Mike Shetzline again. Maybe
5 I'll address the first part and have Dr. Edwards
6 address the clinical practice question.

7 So in terms of the indication
8 statement -- we can put the indication statement up
9 again, that's fine; slide up -- the pursuit of the
10 intolerance or inadequate response to NSAIDs or
11 colchicine is in the current indication because
12 that's this phase 3 development program that we
13 studied, the population we studied. And the reason
14 for that is we also wanted to do -- gouty arthritis
15 being a very morbid and significantly painful
16 disease, we wanted to have an active comparator.
17 And so we chose steroids as that active comparator
18 in order to achieve superiority to steroids, and we
19 did achieve superiority to steroids.

20 So we can't really talk about a steroid-
21 resistant population in our phase 3 programs. We
22 don't have data in steroid-resistant population.

1 So the indication is based on the population we
2 studied.

3 Now, I'm going to have Dr. Edwards address
4 how that could be pursued in clinical practice.

5 DR. EDWARDS: Dr. Edwards. I think what
6 we're not looking at is steroid resistance as an
7 indication. Most people respond somewhat to
8 interarticular, intermuscular, or oral steroids.
9 What we're looking here are patients that just
10 bother all of us when we see them because of the
11 amount of steroids we're going to have to be giving
12 them, repeatedly in many cases.

13 So rather than talk about the steroids being
14 ineffective, it's really the relative
15 contraindication in a given patient to have them on
16 multiple doses of fairly good doses of steroids.
17 So the typical dose that we talk about for treating
18 gout is frequently 35 milligrams daily for 4 days,
19 and then decrements of that over the next
20 12 to 14 days, which on average leaves you with a
21 2-week average dose of steroids of about 25 to
22 26 milligrams per day.

1 This is not insignificant in a number of our
2 patients, and these are the patients that I
3 personally sweat when I see that they aren't able
4 to take the nonsteroidals or the colchicine. I'm
5 not convinced that they wouldn't respond to
6 steroids. I just simply don't want to use them for
7 metabolic and other health reasons.

8 DR. O'NEIL: Thank you.

9 DR. SUAREZ-ALMAZOR: Just a comment. I
10 understand what you're saying, but that's not
11 reflected in the indication, the repeated doses of
12 steroids and so forth. And your own data shows
13 that the 40 milligrams of triamcinolone were as
14 effective in about I think it was 50 percent or
15 60 percent of the patients, just single dose.

16 DR. SHETZLINE: Yes. As I already alluded
17 to, the patient population we chose was to include
18 the active comparator, and the end result of the
19 study was superiority to steroids. But, again,
20 maybe I can have Dr. Wortmann add to the clinical
21 practice.

22 DR. WORTMANN: I think if they had studied

1 the patients that steroids had caused complications
2 or were contraindicated, they'd have to do a
3 placebo-controlled trial. And I think this was a
4 better trial for the patients. But I think it's
5 the total burden of steroids that are going to be
6 considered -- not that they wouldn't work, but you
7 can't give people -- make them Cushingoid, make
8 their diabetes worse, or hypertension worse, or
9 fluid retention worse, give them osteoporosis,
10 osteonecrosis, proximal muscle weakness, skin
11 rashes, and increased risk of infection, all the
12 things that Cushing patients get. Those can be
13 spared, whereas now they're the only alternative
14 for the people who can't take colchicine or
15 nonsteroidals.

16 DR. O'NEIL: Thank you. We are running
17 behind. Therefore, we will take a brief 10-minute
18 break and reconvene at five minutes before the
19 hour.

20 Panel members, I need to remind you to
21 please refrain from discussing the contents of the
22 meeting during the break among yourselves or with

1 members of the audience.

2 (Whereupon, a brief recess was taken.)

3 DR. O'NEIL: Thank you. I'd like to remind
4 you again to silence your telephones and other
5 mechanical and electronic devices.

6 We will now begin the FDA presentations.
7 The first speaker is Dr. Larissa Lapteva, a
8 clinical reviewer at CDER FDA.

9 **FDA Presentation - Larissa Lapteva**

10 DR. LAPTEVA: Good morning. The advisory
11 committee members, FDA, industry representatives,
12 all the meeting participants, my name is Larissa
13 Lapteva, and I work in the Division of Pulmonary,
14 Allergy and Rheumatology Products in the Office of
15 New Drugs in CDER.

16 So in the NDA presentation today, I will
17 give you an overview of the regulatory history and
18 the clinical development program for the biological
19 agent canakinumab, which was developed for
20 treatment of acute attacks of gouty arthritis in
21 this development program. Dr. Ruthanna Davi, the
22 statistician from the Office of Biostatistics, will

1 then discuss the dose selection part in the
2 efficacy findings in this program, after which I
3 will present the overall efficacy conclusions, the
4 summary of safety, and the risk/benefit
5 considerations for canakinumab in treatment of
6 gout.

7 As many of you who are present in this room
8 know, the treatment of gout is founded upon chronic
9 management of hyperuricemia, generally achieved
10 with dietary modifications and urate-lowering
11 agents in patients with recurrent attacks of gouty
12 arthritis. Anti-inflammatory medications such as
13 nonsteroidals, colchicine, or corticosteroid
14 formulations could be used both as a short-term
15 symptomatic treatment of a flare of gouty arthritis
16 or as a daily prophylactic treatment to ameliorate
17 frequency and severity of gout flares, for example,
18 upon initiation of urate-lowering therapy.

19 Owing to its mechanism of action and the
20 effects on the inflammasome protein complex, which
21 we have heard about this morning, canakinumab was
22 developed as an anti-inflammatory agent, and its

1 clinical development program was designed to
2 investigate the product's effects in both treatment
3 of acute gout flares and flare prophylaxis.

4 The part of the clinical development program
5 which was aimed to investigate the effects of
6 canakinumab in treatment of acute gout flares
7 included a short proof of concept trial, a phase 2
8 dose-ranging trial, which Dr. Davi will discuss in
9 a minute, and two phase 3 control trials, which we
10 already know about, trials 56 and 57, which
11 compared a single 150-milligram dose of canakinumab
12 administered subcutaneously with a single
13 40-milligram dose of triamcinolone administered
14 intramuscularly. The program also included two
15 extensions of the core trials, where patients could
16 be retreated with the study medication upon
17 development of new flares.

18 In the double-blinded extensions, quoted as
19 E1, as you have seen on previous slides from
20 previous presentations, patients were treated
21 according to their original study treatment
22 assignments, and in the open label extensions,

1 quoted as E2, all patients were treated with
2 canakinumab 150 milligrams subcutaneously
3 regardless of the treatment they received in the
4 core and E1 extension parts of the trials.

5 The second part of the clinical development
6 program, the part intended to investigate
7 canakinumab for flare prophylaxis upon initiation
8 of allopurinol treatment, to date includes only a
9 dose-ranging phase 2 trial and its open label
10 extension.

11 Let me now briefly talk about some aspects
12 of the regulatory history of canakinumab and gout,
13 particularly in light of the questions which we
14 received just now from the advisory committee panel
15 members.

16 So as was mentioned previously, canakinumab
17 is an already-approved biological product. It was
18 approved for treatment of cryopyrin-associated
19 periodic syndromes in June of 2009. In November of
20 the same year, the sponsor and the agency held an
21 end-of-phase-2 meeting at which time the design of
22 the phase 3 trials for treatment of acute attack of

1 gouty arthritis was discussed and agreed upon.

2 The two prespecified co-primary efficacy
3 endpoints in the phase 3 trials were discussed, and
4 you know that they were patients' assessment of
5 pain improvement on the visual analog scale from
6 zero to 100 millimeters at 72 hours post-dose and
7 time to a new gouty arthritis flare.

8 Comparator treatment with triamcinolone was
9 also discussed and agreed upon at the time, and due
10 to a large number of secondary endpoints, the
11 agency recommended to employ appropriate methods of
12 corrections for multiple comparisons.

13 While not specifically discussed during the
14 end-of-phase-2 meeting, in the pre-meeting
15 correspondence, the sponsor stated their intent to
16 study 150-milligram dose in their phase 3 trials.
17 The agency did not object to the sponsor's dose
18 selection at the time.

19 During the pre-supplemental BLA meeting in
20 June of 2010, it was confirmed that the phase 3
21 trials designed to employ canakinumab as an anti-
22 inflammatory treatment of acute flares will

1 constitute the primary evidence of efficacy
2 supporting the proposed indication.

3 So the currently proposed indication is what
4 you see on the slide. However, this indication
5 evolved from the original proposal discussed at the
6 end-of-phase-2 meeting when the applicant initially
7 proposed the indication for acute treatment and
8 prevention of gout flares in patients who could not
9 use both NSAIDs and colchicine.

10 Given the patient population that was later
11 recruited in the phase 3 trials and the evidence of
12 efficacy obtained from these trials, the indication
13 after a few additional redraft proposals evolved in
14 what you see on the slide, currently phrased as,
15 "For the treatment of gouty arthritis attacks in
16 patients who cannot obtain adequate response with
17 NSAIDs or colchicine," followed not by the claim of
18 prevention but by the statement that the product
19 has also been shown to extend the time to next
20 attack and to reduce the frequency of subsequent
21 attacks.

22 It would be important to note that the

1 proposed second part of the current indication, the
2 time extension, does not necessarily reflect any
3 specific disease-modifying properties of
4 canakinumab, but rather constitutes a unique
5 application of the product, with prolonged
6 pharmacodynamic effects to the setting of acute
7 treatment, which results in prolonged inhibition of
8 clinically recognizable inflammation.

9 With this, I will invite Dr. Davi for the
10 discussion of dose selection and the efficacy
11 findings in this program.

12 **FDA Presentation - Ruthanna Davi**

13 DR. DAVI: Thank you, Dr. Lapteva, and thank
14 you to the committee and others for the opportunity
15 to speak with you today.

16 The topics that I will be covering include
17 dose-ranging considerations based primarily on the
18 sponsor's phase 2 study, number 55, which was
19 designed to compare five doses of canakinumab to
20 triamcinolone; as well as a summary of the efficacy
21 of canakinumab resulting from the phase 3 studies,
22 studies number 56 and 57. That summary will

1 include the primary efficacy results, two selected
2 subgroup analyses, and some comments on the
3 statistical reliability of the secondary endpoint
4 analyses.

5 We begin with the dose-ranging study. As
6 you are aware, you are being asked to comment on
7 the dose selection and whether a lower dose of
8 canakinumab needs to be explored. I will provide a
9 brief description of the primary and selected
10 secondary efficacy results for the phase 2 dose-
11 ranging study and comment on the use of statistical
12 significance in this setting.

13 The objective of this study was to determine
14 the dose of canakinumab that led to the same
15 efficacy as triamcinolone for the treatment of
16 acute flares in gout patients who are refractory or
17 contraindicated to NSAIDs and/or colchicine. This
18 study was a parallel-group patient-blinded design,
19 with patients who presented with an acute gout
20 flare for no longer than five days. They were
21 randomized to one of five doses of
22 canakinumab -- 10, 25, 50, 90, or 150

1 milligrams -- or to 40 milligrams of triamcinolone.
2 The sizes of the canakinumab groups were each 28 or
3 29 patients. The size of the triamcinolone group
4 was approximately twice that of the canakinumab
5 group at 57 patients.

6 The primary endpoint for this study was the
7 pain intensity in the target joint at 72 hours
8 post-dose, measured on the zero to 100 millimeter
9 visual analog scale. This endpoint was the same as
10 one of the co-primary endpoints utilized in the
11 phase 3 study.

12 This is a display of the change from
13 baseline in the primary efficacy endpoint. The
14 treatment groups are indicated on the horizontal
15 axis, with canakinumab groups in blue and
16 triamcinolone groups in red. The change from
17 baseline and VAS pain intensity is indicated on the
18 vertical axis.

19 Negative values represent a decrease in pain
20 intensity from baseline. Each of the triangles
21 represent the least squares mean, and each of the
22 treatment groups and the bars represent two

1 standard arrows, approximating a 95 percent
2 confidence interval.

3 The sponsor's analysis indicated that a
4 linear dose-response model was the best fit for
5 this data, with increasing efficacy for increasing
6 doses. A dose of canakinumab with comparable
7 efficacy to that of triamcinolone could not be
8 identified, as it was estimated to be lower than
9 the lowest dose of canakinumab studied.

10 Results for the primary efficacy endpoint
11 were statistically significantly better for the
12 canakinumab 150-milligram treatment group compared
13 to the triamcinolone group, indicated in this
14 figure by a green star. The other canakinumab
15 doses were numerically but not statistically
16 significantly better than triamcinolone. No
17 statistically significant difference between
18 canakinumab dose groups were identified.

19 While statistical significance is useful as
20 a way to quantify the preciseness of a measure,
21 including the variability and sample size involved,
22 statistically significant differences between the

1 canakinumab dose and triamcinolone should not be
2 considered necessary for selection of that dose to
3 be studied further. In fact, requiring a dose to
4 be statistically, significantly better than the
5 comparator in the phase 2 often results in
6 selection of a dose that is higher than necessary
7 in that the phase 3 studies are generally larger
8 and more powerful than the phase 2 studies. Doses
9 associated with numerical, nonsignificant but
10 clinically meaningful, differences in a phase 2
11 study could be proven to be efficacious in a
12 sufficiently large, well-designed phase 3 study.

13 Numerous other secondary endpoints and
14 analyses were undertaken for this phase 2 study.
15 This table provides results for a small set of
16 those endpoints, and is included in this
17 presentation to illustrate that the results
18 observed for many of the secondary endpoints were
19 consistent with those of the primary efficacy
20 endpoint. That is, there were numerically
21 increasing but not statistically significant
22 differences in efficacy with increasing doses of

1 canakinumab, and usually numerical benefits over
2 triamcinolone.

3 The comparison of the 150-milligram dose of
4 canakinumab to triamcinolone was frequently
5 associated with a p value smaller than the usual
6 standard for type 1 error, 0.05, while the other
7 doses were not.

8 I'm moving now to the examination of
9 efficacy resulting from the phase 3 studies. The
10 design of these studies has been previously
11 described by the sponsor, so I will not reiterate
12 that and will go directly to describing the
13 results. First, the patient population.

14 The patient characteristics were generally
15 well-balanced between the treatment groups with
16 both trials. However, it is important to note that
17 only approximately 39 percent of the studied
18 population in trial 56 and only about one-fifth of
19 the trial 57 had known tophaceous gout. About half
20 of the patients in trial 56, and one-third in trial
21 57, were treated with urate-lowering therapy.
22 Almost all of those who were treated received

1 allopurinol. Only a few people received
2 febuxostat, and no one received pegloticase.

3 As you have seen from the previous
4 presentations, the vast majority of the patient
5 population could not use NSAIDs, whereas the
6 population with the most limited treatment options,
7 patients who were not able to use both NSAIDs and
8 colchicine, comprised a minority, 19 and 48 percent
9 of patients in the canakinumab-treated groups in
10 the two trials.

11 As mentioned previously, the first
12 co-primary endpoint was the patient's assessment of
13 pain intensity in the most affected joint measured
14 on a zero to 100 millimeter visual analog scale.
15 The prespecified analysis of this endpoint was a
16 comparison of means, using an analysis of
17 covariance model.

18 Results of this analysis in each trial are
19 shown in this table. FDA interpretation of this
20 data is largely in agreement with the sponsor in
21 that the mean VAS pain score is statistically
22 significantly lower in the canakinumab group than

1 in the triamcinolone group in each study. The
2 benefit of canakinumab over triamcinolone at
3 72 hours post-treatment is estimated to be
4 approximately 10 to 11 millimeters on a
5 100-millimeter visual analog scale.

6 The second co-primary endpoint was the time
7 to first new gout flare. The hazard ratios
8 resulting from the prespecified analysis, a Cox
9 proportional hazards regression model, are
10 statistically significantly smaller than one in
11 both studies, indicating that the risk of the first
12 new gout flare in the canakinumab group is reduced
13 by 55 percent, approximately 55 percent in study 56
14 and approximately 68 percent in study 57, relative
15 to triamcinolone.

16 Kaplan-Meier estimates of the proportions of
17 patients with the first new gout flare at 12 weeks
18 are also provided and illustrate the benefit of
19 canakinumab over triamcinolone. The FDA
20 perspective regarding these data are, again,
21 largely in agreement with that of the sponsor.

22 The Kaplan-Meier estimates throughout the

1 course of the study are provided to supplement the
2 previous table. The number of days post-dose are
3 indicated in the horizontal axis, and the Kaplan-
4 Meier estimates of the probability of the first new
5 flare is shown on the vertical axis. Triamcinolone
6 is represented with the open circles, and
7 canakinumab is represented by the closed circles.
8 The lack of overlap in the Kaplan-Meier curves for
9 the treatment groups illustrates that the
10 canakinumab group has a reduced risk for time to
11 first new flare relative to triamcinolone that
12 consistently develops over the time course of the
13 study.

14 Let's now examine the first of the two
15 subgroup analyses we wish to share with you today.
16 Subgroup analyses are shown pooling studies 56 and
17 57 to provide increased power.

18 The first subgroup analysis was conducted in
19 the subset of patients who were unable to use both
20 NSAIDs and colchicine. As you can see from the
21 table, both co-primary endpoints were statistically
22 significantly in favor of canakinumab in this

1 subgroup. Although not shown on this slide, these
2 results were consistent with the results of the
3 complement of this group, that is, in patients who
4 were able to use either NSAIDs or colchicine, or
5 both, as evidenced by a nonsignificant p value for
6 the treatment by subgroup interaction term for each
7 endpoint.

8 The second subgroup analysis we wish to
9 share with you is shown on this slide and
10 represents examination of the co-primary endpoints
11 in patients who were taking versus those who were
12 not taking concurrent urate-lowering therapy. The
13 results for pain intensity indicate a consistent
14 treatment effect across subgroups, as evidenced by
15 a nonsignificant treatment-by-subgroup interaction
16 term.

17 However, a quantitative treatment-by-
18 subgroup interaction is evident in the analysis of
19 the time to first flare endpoint, with the
20 treatment by urate-lowering therapy use interaction
21 p value of 0.005. As can be seen from the table,
22 the direction of the between-treatment-group

1 results are consistent in the two subgroups.
2 However, patients treated with
3 canakinumab -- excuse me. They are consistent in
4 that patients treated in the canakinumab group
5 experienced fewer flares compared to patients
6 treated with triamcinolone, regardless of the use
7 of urate-lowering therapy. But the magnitude of
8 that benefit is smaller in patients taking urate-
9 lowering therapy.

10 Before I conclude, I would like to mention
11 just a few words about the secondary endpoints
12 since this is an area where the FDA presentation of
13 the data may give a slightly differing perception
14 from that of the sponsor. We are presenting only
15 those secondary endpoints where a multiplicity
16 correction was prespecified, and we are calling
17 these results significant only if they achieved
18 that standard.

19 The sponsor's presentation included results
20 of several secondary endpoints that were not
21 adjusted for multiplicity, or in one case included
22 an endpoint that was planned to be adjusted for

1 multiplicity but was not described in that manner.

2 In these trials, there were two sets of
3 secondary endpoints. The first is shown on this
4 slide and represents four endpoints to which the
5 Bonferroni-Holm correction for multiplicity was
6 prespecified and applied.

7 Taking into account the multiplicity
8 correction, only two out of four of these
9 endpoints, namely, the proportion of patients
10 taking rescue medication during the first week and
11 the median time to at least 50 percent reduction of
12 baseline pain intensity, achieved statistical
13 significance in study 56. These results are shaded
14 in yellow in this table. However, none of the
15 secondary endpoints in this set achieved
16 statistically significant results when you apply
17 the multiplicity correction in study 57.

18 The first line of this table represents the
19 proportion of patients taking rescue medication
20 during the first week. I believe this was
21 presented on slide 54 in the sponsor's core
22 presentation, without comment, to say that the

1 p value of .02 in study 57 would not be considered
2 statistically significant because of the
3 multiplicity correction.

4 The last line of this table, the SF-36 data,
5 was commented upon in response to a question. And
6 I point it out here just to illustrate that there
7 was no statistically significant difference, and
8 very little numerical difference, between treatment
9 groups for this endpoint at this time point.

10 Since all of the other secondary endpoints
11 that are not shown on this slide were not corrected
12 for multiplicity comparisons, claiming their
13 statistical significance would be considered
14 inappropriate.

15 In conclusion, I would like to summarize
16 what I hope I have conveyed to you today. In the
17 phase 2 study, a statistically significant benefit
18 for the canakinumab group relative to the
19 triamcinolone group was generally observed for the
20 150-milligram dose but not the other doses.
21 However, requiring statistically significant
22 differences when choosing a dose is not necessary.

1 If required, it often leads to a dose that is
2 higher than what is needed to demonstrate efficacy
3 in that phase 3 studies are generally larger and
4 more powerful than dose-ranging studies.

5 Regarding the summary of phase 3 efficacy,
6 the FDA is in general agreement with the sponsor
7 that statistically significant benefits in both
8 co-primary endpoints were demonstrated in each
9 study. Also, no differing treatment effect was
10 identified when patients were subgrouped according
11 to whether they were unable to use NSAIDs and
12 colchicine versus those who could use either
13 NSAIDs, colchicine, or both.

14 Importantly, a quantitative treatment by
15 urate-lowering therapy use interaction was
16 identified for time to next flare, indicating that
17 the benefit of canakinumab is smaller in patients
18 taking urate-lowering therapy than those not using
19 urate-lowering therapy.

20 Finally, we discussed secondary endpoints
21 and the need for multiplicity correction and
22 replication in both studies. None of the secondary

1 endpoints that were corrected for multiplicity
2 resulted in statistically significant differences
3 between treatment groups in both studies.

4 Thank you to the committee and others for
5 your attention to this presentation. I would now
6 like to return the podium to Dr. Lapteva, who will
7 provide closing comments on efficacy and
8 presentation of the safety and risk/benefit
9 considerations for this application.

10 DR. LAPTEVA: So just to recap the efficacy
11 conclusions here and maybe put some clinical
12 context on the statistical considerations, as you
13 have seen, the two phase 3 trials demonstrated
14 efficacy of canakinumab, given at 150-milligram
15 dose subcutaneously, compared to a single
16 40-milligram dose of triamcinolone delivered
17 intramuscularly, and all of this was in treatment
18 of acute flares of gouty arthritis.

19 While overall improvement from the baseline
20 score of 74 millimeters to the post-baseline of
21 about 22 and 28 millimeters in the canakinumab
22 groups was quite substantial improvement, the

1 statistically significant effect size of
2 canakinumab treatment only modestly exceeded that
3 of a single 40-milligram dose of Kenalog given
4 intramuscularly. The overall difference here was
5 about 10 to 11 millimeters at 72 hours post-dose.

6 None of the groups in the core trials
7 reached the point where 50 percent of subjects
8 developed a new flare. Therefore, an actual time
9 to flare could not be estimated in the core trials.
10 The observed difference in flare probability over
11 time was not unexpected, given the prolonged
12 pharmacodynamic effects of canakinumab.

13 It would also be important to emphasize here
14 that these efficacy findings primarily represent
15 clinical symptomatic benefits of an anti-
16 inflammatory treatment during an acute attack of
17 gouty arthritis. Also, notably, the majority of
18 patients who were enrolled in the phase 3 trials
19 were primarily those who could not tolerate
20 nonsteroidals. Patients who could not tolerate
21 both colchicine and nonsteroidals comprised only a
22 minority, 19 percent in study 56 and 48 percent in

1 study 57. Yet, still, in this subgroup when the
2 data were pooled from the two trials, the efficacy
3 of canakinumab was consistent with the overall
4 efficacy results.

5 Also notable, that only about 39 percent of
6 the study population in trial 56 and only about
7 one-fifth in trial 57 had known tophaceous gout,
8 which may not be very consistent with what we
9 normally view as a refractory chronic tophaceous
10 gout population that would be refractory to most of
11 the available therapies.

12 So with this, let me move on to the efficacy
13 findings. The overall safety database for the gout
14 population, as you have noticed, contained double-
15 blind safety data generated from the two dose-
16 ranging controlled trials, 55 and 51, and the two
17 phase 3 controlled trials, 56 and 57, as well as
18 their double-blinded extensions quoted as E1.

19 For the purposes of the presentation, the
20 safety data were pooled by the dose. And although
21 there were several dose groups, as you have seen on
22 the sponsor's slides and as you will see in the

1 tables presented in the subsequent slides here, the
2 primary comparison was made between the proposed-
3 for-marketing 150-milligram canakinumab dose and
4 40-milligram triamcinolone dose.

5 Just to give an upfront disclaimer, the
6 observed signals were generally consistent between
7 the analysis derived from the overall safety
8 database and the separate analyses derived from the
9 phase 3 controlled trials.

10 Because in the gout safety database the vast
11 majority of patients were treated with one
12 injection of canakinumab, it was important to
13 examine safety with retreatment, which as you know
14 came from the core trials, 2356 and 2357, as well
15 as their double-blinded extensions, E1. There were
16 altogether 60 patients retreated in those parts of
17 the trials. And the open label extensions, E2, and
18 up to date we have 118 patients retreated with
19 canakinumab in all three parts of the trials.

20 In addition, safety data on the retreatment
21 came from the open label extension trial, H2251-E1,
22 where 75 patients who were also concurrently

1 treated with allopurinol were retreated with
2 canakinumab on demand. The sponsor also elected to
3 submit additional supportive safety data on 441
4 patients with rheumatoid arthritis who were exposed
5 to canakinumab in their rheumatoid arthritis
6 program.

7 As you see from the table on the slide here,
8 691 patients exposed to canakinumab comprised the
9 database. Of this number, 84 percent were treated
10 with one injection, and 253 patients were treated
11 with the 150-milligram dose and observed for an
12 average of 139 days.

13 Because IL-1 beta is a ubiquitous cytokine
14 and because the original database which supported
15 the approval of cryopyrin-associated periodic
16 syndromes consisted of 104 adult and pediatric
17 patients, it is not unexpected to see more
18 biological effects of canakinumab when examining
19 the much larger database of the gout population.

20 The overall safety findings here with
21 canakinumab have been presented by the sponsor this
22 morning. They have also been discussed in the FDA

1 briefing document. And this presentation will
2 focus primarily on the occurrences of events
3 pertinent to the risk/benefit assessment of
4 canakinumab in gout, which include infections and
5 serious infections, neutropenia and leukopenia,
6 hypertriglyceridemia, uric acid elevations,
7 imbalances in occurrence of renal decline, frequent
8 reporting of hypertension, and of course, safety
9 upon retreatment.

10 Imbalances in occurrences of
11 thrombocytopenia, eosinophil counts, changes in
12 liver function tests, occurrence of vertigo and
13 hypersensitivity reactions, as well as other
14 analysis, have been described in the briefing
15 document, and in the interest of time will not be
16 discussed today in this presentation. So let's
17 first talk about the occurrences of infections and
18 neutropenia.

19 As the sponsor has shown in their
20 presentation, which is consistent with the findings
21 of FDA, the adverse events of infections and
22 infestations were the most common system organ

1 class reported with canakinumab treatment.
2 Infections occurred at the rate of about
3 15 to 19 percent, exceeding the rates observed with
4 triamcinolone. It is again notable here that the
5 infections occurred in the population primarily
6 receiving single injection of the study drug.

7 Serious infections occurred exclusively in
8 the canakinumab-treated patients. Overall, 11
9 events of serious infections occurred in 691
10 exposed patients. Four events of serious
11 infections were reported with the 150-milligram
12 dose of canakinumab, including two events of
13 abscess formation, gastroenteritis, and pneumonia.
14 Although not shown in this slide, in the rheumatoid
15 arthritis program, serious infections again
16 occurred exclusively in the canakinumab-treated
17 patients, and they occurred at a rate of
18 2.7 percent compared to no serious infections
19 observed in the placebo groups.

20 One death of pneumonia occurred in a patient
21 participating in trial 56 during the second open
22 label extension part. This patient developed an

1 acute episode of pneumonia on day 48 following the
2 second injection of canakinumab, which he received
3 on demand in the extension trial. In the RA
4 program, you have also seen that there was one
5 death that occurred due to a wound infection in a
6 patient with intestinal rupture.

7 Several patients in both the rheumatoid
8 arthritis and gout programs experienced infections
9 and serious infections while their peripheral white
10 blood cell counts decreased following the study
11 treatment. Two such cases occurred in the gout
12 program, including a case of serious infection of
13 mandibular abscess and acute respiratory tract
14 infection, and three cases occurred in the
15 rheumatoid arthritis program.

16 Let's now examine the occurrences of
17 leukopenia and neutropenia. Leukopenia and
18 neutropenia are known effects of IL-1 blockades.
19 They are described in the labels of the marketed
20 IL-1 blockers. The table in this slide shows the
21 proportions of subjects whose white blood cell and
22 neutrophil counts decreased with treatment

1 according to the common toxicity criteria grading
2 in different dose groups in the gout safety
3 database. The sponsor has shown you this analysis.
4 FDA has requested the sponsor to do the analysis.

5 As you can see in the columns that are
6 depicted in gray, about one-fifth of patients
7 treated with the 150-milligram dose of canakinumab
8 developed grade 1 leukopenia and neutropenia,
9 compared to about 5 to 6 percent ballpark rates in
10 patients treated with triamcinolone.

11 Fewer patients developed grade 2 and 3
12 decreases, which again were imbalanced towards
13 canakinumab. The majority of subjects who
14 developed leukopenia would develop it within the
15 initial days to a few weeks of treatment. These
16 laboratory changes appeared reversible.

17 Now, when examining the dose response
18 here -- let's see if I could show you. Well, you
19 need to look at the first column. Apparently this
20 pointer isn't working very well. So when examining
21 the dose response, fewer subjects who received less
22 than 100-milligram doses of canakinumab developed

1 leukopenia at the rates only slightly exceeding the
2 rates observed with the comparator groups.

3 Now, let's discuss the occurrence of
4 hyperlipidemia. It is known from the previous
5 experience, again, with the IL-1 blocking agents
6 that IL-1 blockade is associated with increases in
7 serum lipids. Current labeling for IL-1 blockers
8 includes recommendations to monitor for lipid
9 elevation and to institute appropriate treatment
10 when clinically indicated.

11 Of the lipid changes observed with
12 canakinumab, and they're all described in the
13 briefing document, some of them there were very
14 mild differences. But the most prominent were
15 increases in triglycerides. The upper part of the
16 slide shows the table with proportions of subjects
17 shifting to different levels of triglyceride
18 elevation occurring with different canakinumab
19 doses, and the lower part here depicts mean changes
20 in triglycerides for the 150-milligram dose and for
21 the triamcinolone group.

22 Both analyses demonstrate elevations in

1 triglyceride with canakinumab treatment, more so
2 than with triamcinolone treatment, with an average
3 increase of about 33 milligrams per deciliter in
4 the canakinumab group. And it's up to you to judge
5 its clinical significance. It's interesting,
6 though, the canakinumab and triamcinolone really go
7 in different directions here.

8 Let's now move on to one unexpected finding
9 in this development program, a finding that's
10 particularly concerning in the gout population,
11 changes in serum uric acid. While some
12 fluctuations in serum uric acid may be expected
13 with the development of an acute attack of gouty
14 arthritis, the sponsor very eloquently told you
15 about it. However, in this development program,
16 all patients were really flaring at baseline, and
17 yet the difference in the uric acid levels was
18 still seen between the two treatment groups in the
19 randomized setting in both trials.

20 Serum uric acid was measured at different
21 time points in both controlled phase 3 trials.
22 This slide shows mean changes in the levels of

1 serum uric acid from the baseline throughout the
2 12-week observation period in the randomized trial
3 H2356. The canakinumab group here is depicted in
4 blue, whereas triamcinolone is depicted in red.

5 As can be seen, the group means go in quite
6 different directions, and at the time points
7 depicted here with the star marks, the between-
8 group differences become statistically significant.
9 The pattern of serum uric acid elevation with
10 canakinumab appears as a quick increase, as you can
11 see, peaking within the first several days and
12 gradually reaching a plateau towards the end of the
13 study, which would be the 12-week time point for
14 the majority of the patients.

15 It is notable also that in the canakinumab
16 groups, the overall mean changes remain different
17 from the triamcinolone curve and above the
18 pretreatment baseline throughout the observation
19 period. It is also worth to point out that the
20 magnitude of elevation here appears quite modest by
21 the analysis of the means. The numeric changes in
22 milligrams per deciliter are provided in the

1 briefing document. They cannot be seen from this
2 slide, but they're very small.

3 A similar analysis, but for the trial of
4 H2357, is shown on this slide. A similar pattern
5 of serum uric acid elevation is observed with
6 canakinumab. The two curves remain separated with
7 higher levels seen with the canakinumab treatment.
8 Now, given the variability of individual changes
9 that may be overlooked in the analysis of means,
10 proportions of patients with different degrees of
11 serum uric acid increases were examined in both
12 trials.

13 As you can see from the table here, the
14 proportions of subjects with different degrees of
15 elevation in serum uric acid, more subjects who
16 received canakinumab compared to those who received
17 triamcinolone in each of the phase 3 trials and in
18 the combined data had on-treatment elevations of
19 serum uric acid above .5, 1, and 2 milligrams per
20 deciliter. And you can also see that 31 percent of
21 patients who received canakinumab at the dose of
22 150 milligrams had uric acid elevated, 2 milligrams

1 per deciliter or above. You can also see that the
2 odds ratios for the differences here were ranging
3 between 2 and 3.

4 So this slide is very similar to what the
5 sponsor has shown you. It's just a different
6 magnitude of the grading here. So the graphical
7 representation on this slide depicts the changes in
8 the serum uric acid in the two treatment arms
9 combined from the phase 3 trials in patients who
10 were and who were not taking the urate-lowering
11 treatment.

12 The blue lines represent canakinumab
13 treatment, and the red lines represent
14 triamcinolone treatment. The solid lines represent
15 mean changes for patients receiving the urate-
16 lowering treatment, and the dotted lines represent
17 mean changes for patients not receiving the urate-
18 lowering treatment.

19 As you can see, the lines do get separated
20 again with the same pattern. Elevation of serum
21 uric acid is observed with canakinumab treatment
22 regardless of the concomitant urate-lowering

1 therapy, although it appears less pronounced with
2 the allopurinol treatment. The majority of
3 patients were receiving allopurinol here for the
4 urate-lowering therapy.

5 Now, the magnitude of the elevation at the
6 highest point here -- unfortunately, I can't show
7 this to you, but it's the top blue line -- that
8 point is about .6, .7 milligrams per deciliter.
9 Now, these modest but tangible elevations in serum
10 uric acid raise a question about, actually, the
11 long-term outcomes and the possibility of escape
12 from the effects of urate-lowering treatment in
13 patients receiving canakinumab. And,
14 unfortunately, we can't answer that question at
15 this point with the data that we have at hand.

16 Let me now move on to discuss the occurrence
17 of renal decline. As has been previously
18 mentioned, three serious adverse events of renal
19 failures were reported in the canakinumab groups
20 treated with the doses of 150 milligrams or higher
21 compared to no events in the comparator groups.
22 None of the three subjects required hemodialysis,

1 and all of them, as the sponsor correctly
2 indicated, had predisposing comorbid conditions.

3 Nonetheless, given the previously discussed
4 observed changes in serum uric acid and the
5 frequent reporting of hypertension, which I will
6 discuss later, it would be worth to look at the
7 changes in renal function in both treatment arms in
8 the controlled trials. This is something that
9 wasn't shown on the slides previously; what you've
10 seen was the overall safety database on the gout
11 population. So these are the data from the
12 controlled trials.

13 The table in the slide shows proportions of
14 subjects in both trials who developed serum
15 creatinine elevation and a decline in creatinine
16 clearance while they were in study by the 12- and
17 24-week time points. The comparisons here are
18 presented for each of the trials and for the
19 combined data, and the combined data are framed in
20 red.

21 As you see from the table on the slide,
22 greater proportions of patients had elevated

1 creatinine to equal or above 1.5 proper limit of
2 normal, and more subjects had 25 percent or more
3 decline in creatinine clearance in the canakinumab
4 groups compared to the triamcinolone groups in both
5 trials.

6 Now, these specific categorical breaks for
7 the parameters of creatinine and creatinine
8 clearance decline were those that were prespecified
9 in the protocols. This was something that was put
10 up front in the protocols as to how safety will be
11 evaluated.

12 Now, not to overstate the observation here,
13 it will be fair to say that the differences within
14 each trial are driven by the small numbers. But
15 the trends are notable in both trials, and the
16 signal appears more prominent when the data are
17 combined.

18 While these results from the controlled
19 trials, they're shown on the slide, a similar but
20 more subtle signal was also observed in the overall
21 safety database in the gout population. And that's
22 what you've seen with the sponsor showing you. I

1 believe it was slide 83.

2 So besides the unexpected changes in uric
3 acid, hypertension was one of the three most
4 frequently reported events occurring with
5 canakinumab treatment in the gouty arthritis data
6 set, and its frequency seemed to be a bit higher in
7 the higher dose group, as you can see here. But,
8 again, the differences are really driven by the
9 small numbers.

10 Hypertension was also the most common
11 adverse event reported in the combined data from
12 the controlled phase 3 trials on gout, and the most
13 common event reported upon retreatment with
14 canakinumab. In each of these analyses, rates of
15 hypertension were slightly higher than those
16 reported with triamcinolone.

17 Consistent with this frequent reporting was
18 the prespecified in the protocol analysis of
19 proportions of patients with greater than
20 25 percent increases in systolic and diastolic
21 pressure. Not consistent with this analysis were
22 the analysis of the mean changes, where you saw

1 that the overall mean blood pressure change of both
2 systolic and diastolic were changing about the same
3 as the triamcinolone group was changing and in fact
4 decreasing slightly.

5 So on one hand, this frequent reporting in
6 occurrences of blood pressure elevation would not
7 be inconsistent with the comorbid background of the
8 treated population as well as the acute setting in
9 which the treatment was delivered. On the other
10 hand, increases in blood pressure combined with the
11 observation of serum uric acid changes and the
12 observed imbalances in renal decline raise a
13 concern of the overall net effects of canakinumab
14 in the gout population.

15 So as was mentioned earlier, some data were
16 available to aid assessment of safety upon
17 retreatment. The original submission included data
18 on 60 patients retreated in the core and double-
19 blinded extension E1 trials, and they are shown
20 here in the first column.

21 The vast majority of the retreated patients
22 received canakinumab twice during the observation

1 period of 24 weeks. An additional 58 patients
2 received retreatment in the open label extensions
3 E2. And altogether, as I've mentioned, there are
4 118 patients who received retreatment, and the
5 majority of them received two injections of
6 canakinumab.

7 Sixty-seven patients were switched from
8 triamcinolone to canakinumab in the second
9 extensions. Overall, patients who required
10 retreatment appeared to have more polyarticular
11 involvement, and greater proportions of them had
12 tophaceous gout. Notably, fewer retreated patients
13 appeared to have baseline comorbid conditions of
14 hypertension and hypertriglyceridemia.

15 Now, this slide shows the most common system
16 organ classes and adverse events reported among
17 patients retreated in the double-blinded setting in
18 the core and extension E1 parts of both trials.
19 The rates of events among retreated were higher
20 than the rates of events among patients who
21 received canakinumab only one time. Infections and
22 hypertension remained the most frequently reported

1 with retreatment. The rate of the laboratory
2 investigation abnormalities was also higher among
3 retreated subjects.

4 As shown in the FDA briefing document and
5 not included in this slide, a similar pattern of
6 adverse event occurrences were observed with
7 examination of safety upon the retreatment in trial
8 H2251 E1, where canakinumab retreatment was given
9 on demand to patients concurrently treated with
10 allopurinol.

11 Here comes the tricky part. So with the
12 submission of the 120-day safety update, the
13 sponsor made the interim analysis of safety data
14 for the second open label extension, E2, available
15 to the FDA. Given the differences of treatment
16 duration and switching from triamcinolone to
17 canakinumab, FDA requested an analysis of the
18 exposure-adjusted rates of events with the given
19 treatment.

20 Now, these data are currently under review,
21 and the overall preliminary assessment is
22 consistent with the previously observed signal; yet

1 still, I do have one table to show you here, just
2 to give a general overview of what's happening with
3 these patients.

4 So this table includes the data on 118
5 patients that were retreated with canakinumab to
6 date. These data came in late; they were not
7 included in the briefing document. The table may
8 appear to be a little complicated to you, but let
9 me walk you through the data here.

10 So the upper part of the table includes
11 exposure-adjusted event rates for any adverse
12 events, for events of infections, and for events of
13 hypertension. The lower part of the table includes
14 proportions of subjects with the laboratory changes
15 of interest, namely, decreases in white blood cell
16 counts, neutrophils, and increases in creatinine
17 and glomerular filtration rate, decline of
18 glomerular filtration rate.

19 Now, looking horizontally, the first column
20 here is the group of patients who were treated with
21 canakinumab only once. The second column includes
22 118 patients who were treated with two or more

1 injections of canakinumab during the core E1 and E2
2 extensions in both trials.

3 Now, upon crude descriptive comparison, it
4 appears that patients retreated with canakinumab
5 had higher rates of events in the laboratory
6 changes. Now, the yellow part of the table expands
7 on the safety of this retreated group, which
8 includes 118 patients. And you see the event rates
9 in the laboratory changes before they received
10 retreatment and after the first, second, and third
11 retreatment for those who received more injections
12 of canakinumab.

13 Now, upon this within-group comparison, the
14 comparison that the sponsor and we also look at
15 would be the before first retreatment for the 118
16 patients and after first retreatment for the 118
17 patients. And you see that the trends of any
18 adverse events appear to be slightly lower.
19 Infections appear to be probably the same, maybe
20 slightly lower. Hypertension increases slightly.
21 White blood cell count and neutrophil counts remain
22 the same, slightly decreased, maybe. And then

1 creatinine and decline of glomerular filtration
2 rate increases.

3 The sponsor has shown you the data on this
4 group of 43 patients who received three injections
5 of canakinumab. And they had the data for this
6 specific group before they were treated with
7 canakinumab and after they were treated with the
8 second treatment and the third treatment. So there
9 wasn't much that could be seen there. The numbers
10 are very small. But there doesn't appear to be an
11 increase in adverse events there.

12 Now, just to point out that no matter how
13 one looks at the within-treatment group
14 comparisons, these data are very limited,
15 particularly in the sense of the very small number
16 of patients who received three or more injections
17 of canakinumab. And, obviously, this is very far
18 from real life, where patients, if they were to
19 receive canakinumab, would have received quite a
20 number of injections for recurrent gout attack
21 treatment.

22 Also, to point out that changes consistent

1 with the previously observed canakinumab's effects
2 were seen upon switch from triamcinolone to
3 canakinumab. I have a backup slide about it if
4 you'd like to see it.

5 So, in conclusion, the safety profile of
6 canakinumab in the gout population includes all of
7 the observed effects listed on the slide. Some of
8 them have just been discussed in this presentation,
9 and the analysis of all were included in the FDA
10 briefing document.

11 This brings us to the risk/benefit
12 considerations.

13 Dr. Yim has shown you the slide before. It
14 in general summarizes the overall concerns that
15 were raised in the presentations this morning.
16 And, in conclusion, I would like to say that
17 biological therapies, when they were first approved
18 in the period of the 1990s, they really have
19 revolutionized the approach to treatment of
20 rheumatic diseases. They are not without
21 toxicities, but they have been and remain to be
22 valued not only for their clinical symptomatic

1 benefits but also for their disease-modifying
2 effects.

3 The application that we have under
4 discussion today doesn't represent the same
5 risk/benefit setting. The proposal that we have on
6 the table is a new paradigm of applying a
7 biological agent with all of its characteristic
8 side effects to symptomatic, mechanistically
9 targeted treatment of inflammation due to crystal-
10 induced arthritis without improving the root cause
11 of crystal formation, hyperuricemia.

12 While canakinumab is effective as a
13 symptomatic anti-inflammatory treatment of gout
14 flares, the available data do not shed much light
15 on the long-term effects of the product when it is
16 used as chronic intermittent treatment, or with
17 other urate-lowering therapies like febuxostat and
18 pegloticase, or in patients with chronic tophaceous
19 gout that's truly refractory to all of the
20 available therapies.

21 Also, as you have heard today, because both
22 phase 3 trials were done with only a 150-milligram

1 dose, it remains unknown whether a lower dose would
2 have had a different risk/benefit profile.

3 With this in mind, we ask the advisory
4 committee to address in their discussion the
5 risk/benefit profile of canakinumab at the dose,
6 150 milligrams, and to discuss whether the benefits
7 of an anti-inflammatory treatment of acute attacks
8 of gouty arthritis would outweigh the risks of the
9 prolonged IL-1 blockade.

10 On this note, I'd like to thank you for your
11 attention, and this will conclude the FDA
12 presentation.

13 **Clarifying Questions for FDA**

14 DR. O'NEIL: Thank you.

15 We will now proceed with discussion,
16 questions for the FDA regarding their
17 presentations. And as people are deciding whether
18 they have questions or not, I did have one question
19 for Dr. Davi.

20 Why didn't the FDA object to the
21 150-milligram dose as a single study dose to be
22 used in the phase 3 trials at the end of the phase

1 2 meeting?

2 DR. DAVI: That's a difficult question. I
3 actually don't think I'm the person to answer it.
4 I'm going to hand that to my clinical colleagues.

5 DR. OKADA-YIM: Yes. This is Sarah Yim. So
6 I think what we're seeing is sort of a slightly
7 different philosophy. The RA drugs, when they were
8 first developed, the biologics, were developed
9 along the oncology drug line, where people were
10 essentially looking for maximum tolerated doses.

11 That sort of led to kind of a hands-off
12 approach from a regulatory aspect for dose-ranging.
13 I think with the increased attention to safety that
14 we're having in recent years, we're trying to put
15 more emphasis on better dose-ranging. But this was
16 a product of kind of the old style of regulatory
17 management that we had.

18 DR. O'NEIL: Dr. Felson?

19 DR. FELSON: I have a question either for
20 the FDA or the sponsor, which is, can we get any
21 insights into the risk of repeated injections by
22 the other programs that are going on for

1 canakinumab, rheumatoid arthritis, where there were
2 repeated injections, and maybe CAPS and maybe
3 cardiovascular disease where it sounds like there's
4 more safety experience? Were the adverse events
5 that occurred, the infection risk, were they
6 similar with longer-term treatment? Did they
7 increase with longer-term treatment?

8 DR. SHETZLINE: If I could have this slide
9 up, we can show you the long-term safety data for
10 the RA program. And you can see on this slide that
11 this is again the same data set we discussed
12 earlier. That's the all-RA data set. There are
13 two slides in this group. But these are just a
14 total of serious adverse events and the chronicity
15 of that, 441 patients in total. And, again, this
16 is the cohort, the RA program, where they had
17 between 150 and 300 milligrams every 2 to 4 weeks
18 repeated dosing out to 144 weeks in some cases.

19 So in this setting, we don't necessarily see
20 a significant increase in SAEs as the chronicity of
21 the program moves forward.

22 DR. FELSON: Sorry. Can I just ask, so

1 those are not cumulative numbers. They are -- I
2 see. So they are rates within each of those
3 intervals.

4 DR. SHETZLINE: Correct.

5 DR. FELSON: Got it. Thanks.

6 DR. SHETZLINE: Okay. Slide down.

7 DR. O'NEIL: The next question is from
8 Dr. Buckley.

9 DR. BUCKLEY: I'm curious about the
10 agreed-upon endpoint, one of them being 72 hours.
11 When I'm taking care of patients with gout, I think
12 the thing they want me to do is get their pain
13 under control, hopefully within an hour, certainly
14 within a day, and then to maintain that over a
15 period of time.

16 The 72-hour time point I was curious about.
17 Now, I know the FDA asked that a 24-hour time point
18 also be looked at. I wonder, and I don't know the
19 answer to this, if there's some mismatch in how
20 this drug works in terms of time to get maximum
21 effect, and that it looked like it took about seven
22 days to get maximum effect. And until you pushed

1 it to the high dose, you didn't get about a
2 50 percent release in that first 24 hours.

3 Ideally, I think what you'd want is a drug
4 that's working quickly, off when you don't need it
5 any more, and then you can turn on quickly again.
6 And it seems that one of the challenges here is a
7 drug that you might have to get to higher dose to
8 get that 24-hour effect, and then for some patients
9 to keep that effect for three months, or months,
10 may be optimal; for other patients unnecessary.

11 Do you think -- I mean, from looking at this
12 data, do you think there's something to do with the
13 timing of how this drug works that means we have to
14 push it to these high doses?

15 DR. LAPTEVA: We'll let the sponsor respond,
16 and then we have two slides, one in response to
17 your question and then another in response to the
18 previous question.

19 DR. GATLIN: Thank you. Gatlin, Novartis.

20 Could I have the slide up, please? So one
21 of the measures that we did do is we did assess the
22 efficacy in terms of lowering this acute pain from

1 that baseline pain of 74 millimeters on the zero to
2 100 visual analog scale. And as you rightly
3 pointed out, these are patients who really want
4 quick relief from their pain. And as early as six
5 hours, there is a 16-millimeter decrement in the
6 pain score with canakinumab that is greater than
7 that seen with triamcinolone; and at every time
8 point in the observation period, there was
9 clinically significant and meaningful reductions in
10 pain.

11 I'd also like to -- when you mentioned the
12 longer-term benefit in terms of who needs which
13 benefit -- remind the committee that there
14 was -- 72 percent of patients were attack-free for
15 six months. And this was a population of very
16 frequently flaring patients.

17 DR. LAPTEVA: So we also have looked at the
18 changes as early as 6 hours and 12 hours and
19 24 hours. They were consistent with the primary
20 efficacy endpoint.

21 If you could please show the backup slide
22 number 25. It should be slide number 45. It

1 should be the very first slide following the
2 presentation.

3 So here you see the pharmacodynamic effect
4 of canakinumab. And this is something that our
5 pharmacologist looked at. This is IL-1 beta
6 suppression following the single 150-milligram
7 dose. You see that the suppression goes right
8 away, within the first day or two, and then it
9 remains up to 60 days at different degrees.

10 Then if you could show the very last slide
11 off the backups.

12 So this is just an attempt to look at the
13 long-term data, and these are exposure-adjusted
14 incident rates of infections and serious infections
15 in gout and the RA population. And this is in
16 response to Dr. Felson's question.

17 As you can see, the incidence rates per
18 100 patient years do increase with chronic
19 treatment in both infections and serious
20 infections. Granted, the background risk for RA
21 and gout populations are probably different. Yet
22 still, from this very limited data, you could see

1 that the longer exposure leads to somewhat higher
2 incidence rates, although notably here, canakinumab
3 and placebo for the overall infections look very
4 similar in the RA program.

5 DR. OKADA-YIM: I just want to clarify also
6 that experience with these biologics over time, in
7 the open label extensions, people who aren't
8 tolerating the medication because of infections or
9 whatever, they drop out. So you may not see an
10 increase in the proportions, but the patients are
11 dropping out who are experiencing those adverse
12 events.

13 Then to get back to Dr. Buckley's question,
14 I think there was attention about when we wanted to
15 see the primary endpoint taken, and we did express
16 those concerns to the sponsor. I think they were
17 interested in having a slightly longer time point
18 because, as was mentioned, the drug has kind of a
19 long onset and longer offset.

20 So I think there were -- well, they can
21 speak for themselves. But 24 hours, I think, was
22 kind of an iffy time point for them, but we did ask

1 them to get data on that.

2 DR. O'NEIL: Dr. Felson, I believe, wants to
3 pursue his question. Well, we have several other
4 people waiting, so only pursue that question.

5 DR. FELSON: Fine. Thanks.

6 I guess I wanted to ask, if I could, it
7 sounds to me something that is not necessarily like
8 the other biologics, which I wanted to clarify. So
9 in TNF inhibitors, data have now shown fairly
10 convincingly that those who are going to get into
11 trouble get into trouble within the first 6 months
12 or so of usage. And then those who remain and
13 survive that period of use, frankly, don't have
14 much of a risk after that.

15 This doesn't sound like that. This sounds
16 like the risk is cumulative. So you get a group of
17 people that get into risk with serious infections.
18 They get eliminated because they don't get the drug
19 any more. Then you get another group of people who
20 get infections. And so that 2 percent with each of
21 those intervals is a cumulative percent risk.

22 So if you add each of those -- as there were

1 five intervals there -- serious infection rates
2 after 72 months of use is now 10 to 12 to
3 15 percent, which is not what it is, I think, for
4 TNF inhibitors.

5 I guess I wanted to -- that's a tough
6 statement. And I guess I wanted to ask the
7 sponsor, really, to respond to that potential
8 observation.

9 DR. SHETZLINE: I guess the answer -- the
10 primary data set I think would come from the RA
11 data set, which we showed earlier. If you're
12 asking about how the cumulative effects -- maybe I
13 can put this slide up -- the cumulative effects do
14 show out, you can see, as we get further along in
15 the study -- and again, this can be confounded by
16 dropouts or other things. But the event rate does
17 drop off, and it doesn't seem like we see a
18 consistent reporting of the events.

19 If I could have the core slide that we had
20 on the 43 patients. Again, it's a limited data
21 set, and I do understand it's a limited data set.
22 We were somewhat compromised in the program by the

1 durability of efficacy.

2 Can I have the slide up? Actually,
3 similarly, this is the exposure-adjusted data,
4 which you saw on the core presentation. And I take
5 the point that there still could be some similar
6 rates at the intervals. But from a trends
7 perspective in looking at the numbers, the numbers
8 are actually going down. And it's also true if we
9 look specifically again at limited data sets from a
10 standpoint of SAEs, we haven't seen any SAEs in the
11 population who've been treated more than two times;
12 again, a limited data set.

13 So I think in the gouty arthritis data set,
14 it's limited. In the RA data set, it's much
15 larger, but we're not necessarily seeing that
16 cumulative effect.

17 DR. WORTMANN: Bob Wortmann. If I could
18 comment from a clinical perspective, you mentioned
19 RA as a comparator here, and I would argue that
20 this population that this drug would be beneficial
21 for is just as disabled as patients with severe RA.

22 The difference is, though, 72 percent of the

1 people had six months of relief from one injection.
2 So let's say, the worst case scenario, those all
3 flared at six months in one day, and they got
4 another shot, it might buy them another six months
5 of benefit.

6 So I think the amount of people who would
7 get frequent use of this would be a minority,
8 especially because if we're smart enough to be able
9 to use this drug, we should be smart enough to know
10 that we've got to get their serum urate low enough
11 to get rid of the uric acid. And that can take a
12 period of as little as six months in some patients
13 and as long as three years in others. But the goal
14 is to stop using this medicine by doing what it
15 takes to get rid of this disease, which we can do
16 in this disease as opposed to RA.

17 DR. O'NEIL: I would like to remind the
18 sponsor that this is clarification questions for
19 the FDA. So your ability to speak is at the
20 discretion of the FDA.

21 The next question is from Dr. Suarez-
22 Almazor.

1 DR. SUAREZ-ALMAZOR: Yes. I guess I'm also
2 concerned about the potential for retreatment
3 without adequate data. From the data that the
4 sponsor presented, this could be used on 300,000
5 people three, four times a year over a number of
6 years. And we only have data on 43 patients with
7 gout that have received three treatments or more
8 with a drug that apparently has a number of
9 adverse-related events, such as the increase in
10 creatinine, neutropenia, increase in uric acid, and
11 so forth.

12 So my question to the FDA, I didn't
13 understand exactly what the discrepancy in the
14 interpretation of the results was on those 43
15 patients with respect to the sponsor. So I was
16 wondering if you could comment on that.

17 DR. LAPTEVA: Well, it wasn't necessarily
18 the discrepancy. It's just that the table that I
19 had on my slide did not include the data on
20 subsequent retreatment of those specific
21 43 patients. So these two slides, they complement
22 each other, if you will.

1 I only had one column for the 43 patients.
2 There was no extension of what happened with that
3 group prior to injection of canakinumab and then
4 after the first injection, second injection, and
5 third injection, that's what the sponsor has shown
6 on their slide.

7 DR. SUAREZ-ALMAZOR: Okay. But that's prior
8 to the first reinjection. So, again, going back to
9 what Dr. Felson mentioned, the risk was constant
10 for those 43 as far as events. It was not
11 cumulative. That was the slide of the sponsor, I
12 think, not yours, because you didn't have --

13 DR. LAPTEVA: Right.

14 DR. SUAREZ-ALMAZOR: So it was a constant
15 risk for infection after the first treatment, after
16 the second treatment, and after the third treatment
17 for the 43 patients. Right?

18 DR. LAPTEVA: Right. Based on three
19 patients who were the indicator of the infections.
20 They could probably put the slide up if you'd like
21 to take a look at it again.

22 DR. SHETZLINE: Shetzline, Novartis. So

1 this is the adverse events reporting, okay, for the
2 system organ classes. Okay? And what I
3 highlighted were the overall SAEs, the AEs, and you
4 can see the line in the infections. So from an
5 overall safety perspective, as we were talking
6 about event accumulation, looking at the SAEs and
7 the AEs, you don't see that cumulative effect.

8 Now, in regards to the question on the
9 table, from an infection perspective, these are the
10 exposure-adjusted rates. You can see, for
11 infections, 97, 76, and 89. So they are tending to
12 be in a similar range for this data set of 43
13 patients.

14 This would be consistent, obviously, with
15 the labeling we have in terms of the warnings and
16 precautions around infections and serious
17 infections. This is a known labeling for -- at
18 present, it's our CAPS labeling.

19 DR. LAPTEVA: But if you could also mention
20 how many patients are there in the numerator for
21 the infections. I believe there are three or four
22 patients; because this number corresponds for 100

1 patient years incidence rates, but they're actually
2 from three or four patients in each group.

3 If you could clarify, what was the number
4 there?

5 DR. SHETZLINE: Yes. We'll check on that.

6 DR. SUAREZ-ALMAZOR: Okay. And also, if you
7 could clarify whether -- I mean, these are all
8 different patients. It's not the same patient
9 reinfesting over and over.

10 DR. SHETZLINE: So 8 is two patients. So
11 every 4 is one patient. So for the SAEs, that
12 would be six patients. Okay?

13 DR. SUAREZ-ALMAZOR: They are all different
14 patients? I mean, the patients were not dropped
15 out after they retreated, even if they had an
16 infection.

17 DR. SHETZLINE: This is based on events,
18 reported events, not patients.

19 DR. SUAREZ-ALMAZOR: Okay. But the events
20 were all in different patients, or was this --

21 DR. SHETZLINE: This is the cumulative for
22 events reported. So if a patient reported two

1 events, that would be there twice.

2 DR. SUAREZ-ALMAZOR: Okay. But do we know
3 if each event corresponds to a different patient,
4 or it could be just one patient having multiple
5 events? Do we know that?

6 DR. SHETZLINE: That's not evident in this
7 table. But that could be the case. We can find
8 out.

9 DR. O'NEIL: Thank you.

10 We will take one more question in this
11 session, and then following the open public
12 hearing, we will be able to take a few more
13 questions and have more discussion.

14 The next question is from Dr. Gibofsky.

15 DR. GIBOFSKY: This is a corollary of
16 Dr. Buckley's earlier question. I'm mindful of
17 Dr. Edwards' admonition that we should treat pain
18 early in these patients, and Dr. Gatlin's comment
19 that we need to get on top of the pain.

20 So I'm wondering if the agency saw any data
21 in the retreatment population about any differences
22 in the kinetics of pain relief in the retreated

1 patients as opposed to the patients that were not
2 retreated.

3 DR. LAPTEVA: So the sponsor could probably
4 talk more about it. But in a nutshell, what we've
5 seen, the response to pain was very similar in the
6 flares that were subsequent to the baseline flares.
7 What was different was the baseline visual analog
8 scale score, which was about 10 millimeters better
9 than the very first baseline score. But in terms
10 of response, they were responding
11 descriptively -- again, descriptively -- kind of in
12 a similar way.

13 DR. GIBOFSKY: Thank you.

14 DR. O'NEIL: Thank you. We will now break
15 for lunch. We will reconvene again in this room
16 in, I guess, 45 minutes from now, at 1:00 p.m.
17 Please take your personal belongings with you at
18 this time. The room will be secured by FDA staff
19 during the lunch break, and you will not be allowed
20 back into the room until we reconvene.

21 Panel members, I remind you again that there
22 should be no discussion of the meeting content

1 during lunch among yourselves or with any member of
2 the audience. Thank you.

3 (Whereupon, at 12:10 p.m., a luncheon recess
4 was taken.)

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

(1:00 p.m.)

Open Public Hearing

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

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

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

1 if you do not have such financial relationships.
2 If you choose not to address this issue of
3 financial relationships at the beginning of your
4 statement, it will not preclude you from speaking.

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

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

18 If the first speaker for the OPH section
19 could come to the microphone. Thank you.

20 DR. CAROME: Good afternoon. My name is
21 Dr. Michael Carome, deputy director of the health
22 research group at Public Citizen. I am

1 testifying on behalf of myself and Dr. Sidney
2 Wolfe, the director of our group. We have no
3 conflicts of interest.

4 We oppose FDA approval of canakinumab, a
5 potent immunosuppressive agent, for the treatment
6 of patients with gouty arthritis because the drug
7 has serious life-threatening risks that far
8 outweigh the drug's clinical benefits, which are
9 limited primarily to relief of pain from acute gout
10 flares in this patient population.

11 In terms of pharmacokinetics, the peak serum
12 canakinumab concentration occurs at 7 days after a
13 dose, and its half-life is 26 days. In this
14 regard, the FDA noted the following.

15 Canakinumab has a long half-life and
16 extended pharmacodynamic effects. These are not
17 characteristics typical of an acute treatment, and
18 both efficacy and safety data suggest the effects
19 of even a single subcutaneous injection of this
20 drug may be protracted.

21 In terms of benefit, the FDA notes that
22 canakinumab is expected to provide primarily a

1 symptomatic benefit in gout patients. On the other
2 hand, regarding the risk assessment, even though
3 the number of subjects in the gouty arthritis
4 trials was relatively small and most received a
5 single dose of canakinumab, the FDA identified
6 multiple serious safety concerns.

7 The overall percent of subjects experiencing
8 at least one serious adverse event was more than
9 twofold higher in the pool of study patients
10 receiving canakinumab versus those receiving the
11 control, triamcinolone, as shown in the table here.
12 Importantly, among the serious adverse events, the
13 occurrence of serious infections was observed
14 exclusively in the canakinumab-treated group.

15 Given its mechanism of action as an
16 immunosuppressant, canakinumab would be expected to
17 increase the risks of all types of infections. The
18 FDA expressed the following significant concern
19 about this signal of serious infections.

20 "Although the occurrence of infections would
21 not be unexpected with an interleukin-1 inhibitor,
22 the increased rate of the serious infections in

1 gout patients after a single injection of
2 canakinumab is a unique and concerning observation
3 in this development program."

4 The inadequacy of the safety database
5 submitted as a basis for this approval, for
6 canakinumab, contrasts sharply with the much larger
7 amount of long-term safety data submitted prior to
8 the FDA approval of another drug, Anakinra, for the
9 treatment of rheumatoid arthritis.

10 For that approval, data from a safety study
11 with 875 patients, given the drug daily for at
12 least six months, as well as data on several
13 hundred additional subjects in randomized efficacy
14 studies, was submitted to the FDA. In contrast,
15 for canakinumab, only 118 subjects with gout were
16 treated with more than one injection at the
17 proposed dose.

18 Immunosuppressive drugs like canakinumab can
19 impair the body's immunosurveillance and increase
20 the risk of malignancy, particularly with repeat
21 dosing. The duration size of the studies involving
22 subjects with gout did not allow for an adequate

1 assessment of the malignancy risk of this drug.

2 However, the FDA noted the following:

3 "While the data show that the incidence of
4 malignancies is not increased upon single injection
5 treatment with canakinumab administered for gouty
6 arthritis, the available data do not allow an
7 estimation of the potential risk for malignancy
8 upon chronic, repetitive, on-demand canakinumab
9 treatment in the gout patient."

10 Additional abnormalities that the FDA noted,
11 occurring more frequently in patients treated with
12 canakinumab versus patients treated with
13 triamcinolone, included leukopenia, neutropenia,
14 and thrombocytopenia; declines in renal function;
15 elevations in serum triglycerides; elevations in
16 serum uric acid; and liver dysfunction.

17 Novartis estimates that approximately
18 300,000 gout patients will be candidates for this
19 drug if it is approved for this indication, gout.
20 However, it is highly likely that off-label use
21 will result in many more gout patients being
22 treated with this drug. Even with approved use for

1 gout attacks in a patient population of 300,000,
2 repeated dosing with canakinumab will result in
3 large numbers of serious infections and other life-
4 threatening complications.

5 Therefore, we recommend the FDA review
6 concludes that the treatment of whether the
7 benefits of this drug is acceptable for the
8 treatment of acute gout flares is -- they say it's
9 complicated. We disagree. The assessment is not
10 complicated. Like other immunosuppressing
11 monoclonal antibodies, canakinumab is a potent and
12 dangerous drug. While the risks of this drug are
13 justified for patients with the rare disease CAPS,
14 these risks are not outweighed by the symptomatic
15 benefits provided in patients in gout.

16 Therefore, in the interest of protecting the
17 public health, the FDA should not approve this drug
18 for the treatment of gout. Thank you for your
19 attention.

20 DR. O'NEIL: Thank you.

21 Would the second speaker please come to the
22 microphone?

1 MR. WILLIAMS: Thank you, Dr. O'Neil. And I
2 don't have any financial relationships to disclose
3 today.

4 My name is Scott Williams, and I'm vice
5 president of Men's Health Network. Men's Health
6 Network is a national nonprofit organization whose
7 mission is to reach men and their families where
8 they live, work, play, and pray with health
9 prevention messages and tools, screening programs,
10 educational materials, advocacy opportunities, and
11 patient navigation.

12 As you know, gout is a chronic metabolic
13 disease affecting approximately 8.3 million
14 Americans, and is the most common form of
15 inflammatory arthritis in men. Gout can attack
16 silently, even between flares. A gout attack or
17 flare occurs when excess uric acid in the blood
18 begins to form crystals, triggering an inflammatory
19 response in the joints or soft tissue, causing
20 extreme discomfort. Crystals may continuously form
21 and build up in the joints, possibly leading to
22 joint destruction over time.

1 In 2010, we conducted a survey of over
2 1,000 men and women living with gout. The survey
3 evaluated their level of discomfort or pain, the
4 emotional toll of the disease, and how well they
5 understood their condition. Of those surveyed,
6 69 percent described the pain of a gout attack as
7 "miserable," yet a quarter of gout patients feel
8 that those without gout perceive them as
9 overreacting to attacks, and 67 percent feel as
10 though others do not take the condition seriously.

11 Other key findings of the survey included,
12 when we asked to describe the physical sensation of
13 a gout attack, 23 percent of gout patients compared
14 the pain to shattered glass piercing their skin, 28
15 percent to breaking a bone, and 34 percent to a
16 severe burn.

17 The survey also asked patients,
18 theoretically, what would they give up in exchange
19 for never having another gout flare. Thirty-seven
20 percent responded that they would give up winning
21 the lottery, and 22 percent said they would give up
22 a year's worth of vacation time to never have

1 another gout attack.

2 Finally, a third of respondents have
3 experienced an average of two or more attacks in
4 the last 12 months.

5 Gout may run in families, and is more common
6 in males and post-menopausal women. It's also
7 important to note that men over the past decades
8 have shown poorer health outcomes than women across
9 all racial and ethnic groups, as well as
10 socioeconomic status. This can be contributed to
11 several cultural attitudes that have been ingrained
12 in American boys and men for decades.

13 Men are taught at an early age to suck it up
14 and that big boys don't cry. When a boy is 5 years
15 old, falls down, and skins his knee, his mom or dad
16 may tell him to shake it off, but when he's
17 50 years old and experiencing chest pain, he may be
18 told it's indigestion, but it's really the first
19 sign of a cardiovascular event.

20 Really, when you look at it, the situation
21 for men's health overall is dire. Men are leading
22 in 9 out of the top 10 causes of death. The life

1 expectancy gap between men and women has increased
2 from 1 year in 1920 to 5.1 years in 2007. And the
3 Centers for Disease Control studies have shown that
4 women are actually 100 percent more likely to seek
5 preventive healthcare.

6 I say this because, really, the health
7 crisis is also of particular concern, not just to
8 men but also to the women as well regarding their
9 fathers, husbands, sons, and brothers. According
10 to the United States Census Bureau, the ratio of
11 men to women in early retirement years, the age
12 group of 65 to 69, actually reduces from 85 men to
13 100 women.

14 The growing disparity suggests that, among
15 other factors, the declining health of men
16 increases the risk of women as they enter
17 retirement age as widows. According to the
18 Administration on Aging, more than half of elderly
19 widows now living in poverty were not so before the
20 death of their husbands.

21 As we as an organization tackle many of
22 these social, societal, and cultural barriers to

1 health and well-being for men, women, and their
2 families, we must not lose sight of the need for
3 safe and effective treatment options. It is also
4 of critical importance for patients and healthcare
5 providers to work closely together to determine the
6 best treatment plan, given their situation.

7 To conclude, there's an immense need for new
8 and innovative treatment options for gout patients
9 and their families. Today is an important day for
10 men and women who are suffering and will suffer
11 from gout and gouty arthritis, as well as the
12 millions of families and loved ones across the
13 nation who are profoundly affected.

14 I greatly appreciate the opportunity to
15 offer my remarks and presentation, and thank you
16 for your time.

17 DR. O'NEIL: Thank you, Mr. Williams.

18 I'd like to invite the third speaker to the
19 open public hearing.

20 MR. ABRAMS: Dr. O'Neil and committee
21 members, my name is Burton Abrams. I speak for
22 myself about my personal experience with gout. I

1 have no financial relationship influencing what I
2 have to say.

3 For 15 years, I suffered from the severe and
4 debilitating pain of intermittent gout flares in my
5 foot. I experienced inability to diagnose my gout
6 by my primary care physician and by an orthopedist,
7 followed by a preliminary diagnosis by a
8 podiatrist, with final confirmation by a
9 rheumatologist. None of my blood tests showed
10 elevated uric acid levels.

11 During that 15-year period, my use of
12 naproxen, ibuprofen, indomethacin, and various
13 alternative medicine treatments each became less
14 and less effective as time went on, while my
15 overnight gout flares became more frequent. I
16 finally accepted that I would have to begin a
17 lifelong regimen of allopurinol, when a seemingly
18 unrelated turn of events led to the immediate and
19 complete cessation of my gout flares. That was
20 eight years ago. The events led me to be diagnosed
21 with sleep apnea, which I learned to overcome by
22 position therapy, and that stopped my gout. Since

1 that time I have learned, by reading online posts,
2 that others have experienced a similar result.

3 I was astonished to find that almost no
4 physicians were aware of the connection of gout
5 with sleep apnea, despite the fact that most gout
6 flares originate while sleeping and the fact that
7 medical literature had already described how the
8 hypoxia of sleep apnea causes cell catabolism,
9 which culminates in the generation of excess uric
10 acid being fed into the blood; plus acidosis, which
11 reduces the concentration of uric acid which the
12 blood can hold in solution.

13 More recently, medical literature has
14 reported that the hypoxia of sleep apnea reduces
15 kidney function so that removal of uric acid from
16 the blood is slowed. Thus, the hypoxia of sleep
17 apnea affects serum uric acid by increased influx,
18 decreased efflux, and reduced storage capacity, a
19 perfect storm for the precipitation of the
20 monosodium urate crystals which cause gout.

21 Some recent studies have found that gout is
22 accompanied by increased risk for the development

1 of cardiovascular diseases and diabetes. None of
2 these studies gives recognition to the fact that
3 those diseases have already been shown to be
4 consequences of sleep apnea. My own experience was
5 the development of atrial fibrillation and
6 diabetes. The A-fib disappeared within six months
7 of my sleep apnea resolution. The diabetes receded
8 to the point where I can prevent its recurrence
9 strictly by a low glycemic index diet.

10 I greatly regret that no one could tell me
11 at the onset of my gout that it was an early
12 warning of my sleep apnea, which might have allowed
13 me to overcome the sleep apnea and thereby prevent
14 the development of my A-fib and diabetes as well as
15 overcome the gout.

16 There have been no empirical studies
17 published using patient cohorts to establish what
18 percentage of gout sufferers have concomitant sleep
19 apnea and to what degree resolution of their sleep
20 apnea mitigates their gout. I have compiled some
21 statistical information, from which I calculated
22 that at least 50 percent of gout sufferers have

1 concomitant sleep apnea, which is corroborated by
2 my primary care physician's results from screening
3 all his gout patients for sleep apnea, and I can
4 give you his contact information if you want. But
5 this whole line of treatment is presently stymied
6 by the lack of formal patient studies.

7 Allopathic physicians have instead relied on
8 pharmaceuticals and diet modification to treat
9 gout. Recent data have shown that the benefit of
10 diet modification is minimal. What may be most
11 effective is not what pills we swallow, nor how we
12 eat or drink, but how we sleep.

13 Is there some action that this committee or
14 its members individually can take to inform
15 physicians of the importance of screening their
16 gout patients for sleep apnea? Leaving sleep apnea
17 untreated for a long time has been shown to
18 seriously shorten life expectancy. For some
19 people, gout is its early warning.

20 Thank you.

21 DR. O'NEIL: Thank you, Mr. Abrams.

22 The next public speaker.

1 MR. GINSBERG: Hello. I have no disclosures
2 to make today regarding my travel here. The Global
3 Healthy Living Foundation accepts grants and
4 charitable contributions from many pharmaceutical
5 companies, as well as government, private
6 foundations, and individuals. We have not accepted
7 funding from Novartis, the maker of the drug I'll
8 talk about today. We have received scientific
9 briefings from the manufacturer as well as from our
10 independent medical/scientific advisory board.

11 Good afternoon. On behalf of the Global
12 Healthy Living Foundation, I want to thank this
13 committee for allowing me to speak today. The
14 Global Healthy Living Foundation is a 501(c)(3)
15 patient activity group that works to improve the
16 quality of life for people with chronic disease,
17 often focusing on those least likely to advocate
18 for themselves.

19 We focus on several disease states and the
20 people who live with these diseases, including more
21 than 49,000 members of CreakyJoints.org,
22 CreakyBones.org, and RedPatch.org, our arthritis,

1 osteoporosis, and psoriasis patient advocacy
2 groups, respectively. As you know, gout is a form
3 of arthritis, and I'm here today to speak in favor
4 of approving canakinumab for this condition. I
5 should have practiced that one earlier.

6 My name is Seth Ginsberg, and I am the co-
7 founder of Creaky Joints, Creaky Bones, Red Patch,
8 and the Global Healthy Living Foundation. I was
9 diagnosed with spondyloarthropathy at the age of
10 13. By age 15, I was a national spokesperson for
11 the Arthritis Foundation. At 18, when I went away
12 to college 200 miles away from home and in pain, I
13 quickly realized there was a need for positive and
14 supportive communities, experts, and other patients
15 alike with whom to share strength and experience.

16 The virtual community we called Creaky
17 Joints was the result of this realization. In the
18 past 11 years, we have incorporated additional
19 conditions and advocated for patients within the
20 private health insurance, Medicaid, and Medicare
21 communities in order to help ensure access to care.

22 Our guiding philosophy is to create and to

1 support processes that inform patients about the
2 choices they and their physicians have. We believe
3 choice is paramount, and that the objective is to
4 allow choice to an educated patient and physician
5 community so personal medicine as well as public
6 health is best served.

7 Joanne Kathleen Rowling, author of the Harry
8 Potter books, said, "It is our choices that show
9 what we truly are far more than our abilities." As
10 a woman who survived as a welfare mother while
11 writing her books, Harry Potter and the Sorcerer's
12 Stone, she had only choices because the world
13 assumed she had no abilities.

14 Patients, without the ability to treat their
15 own disease, often have limited choices, whether
16 from reduced access to care because of provisions
17 in their private health insurance policies or their
18 own financial inability to participate in the
19 healthcare system as it currently exists. We
20 cannot change all of these things and all of these
21 access to care issues today, but we can increase
22 choice.

1 Patients with chronic diseases, the
2 physicians who treat them, and the family and
3 friends who care for them are often at a loss for
4 effective drugs. This is especially true for
5 people on multiple medications or who have had
6 organ transplants because the medications they take
7 are contraindicated for many of the most popular
8 gout treatments today.

9 We regularly hear from our members who have
10 gouty arthritis, and their pain is our pain. It's
11 all of our pain. Their gout episodes prevent them
12 from being productive members of society. Many
13 times it prevents them from being loving, happy
14 fathers, sons, and brothers. And it prevents them
15 from enjoying a quality of life that they deserve.

16 We are not scientists, but we have seen the
17 clinical trial results of canakinumab regarding
18 gout. And we are, as a patient advocacy group,
19 endorsing it.

20 Thank you all very much for allowing me to
21 speak today. It's good to see you again.

22 DR. O'NEIL: Thank you, Mr. Ginsberg.

1 The last speaker for the open public
2 hearing, please.

3 MR. O'GRADY: Good afternoon. My name is
4 Mike O'Grady of Oakton, Virginia. I'm a private
5 individual living with a kidney transplant and a
6 gout diagnosis. I have no conflicts of interest to
7 report.

8 I would strongly advocate alternatives for
9 the treatment of gout. I come from a family with a
10 long history of polycystic kidney disease, and have
11 watched my dad and his two brothers and three of my
12 five sisters devastated by this disease. I have
13 one adult son who we've elected not to have
14 diagnosed. The great news is that I received a
15 kidney transplant eight years ago from my cousin,
16 and I'm doing great.

17 As a result of my family history, I've
18 always played a proactive role with my disease,
19 choosing to get involved over 30 years ago with the
20 National Kidney Foundation, serving the National
21 Capital Area, having served in many volunteer
22 leadership roles there, including chairman of the

1 board of directors. I believe myself to be an
2 informed consumer.

3 One nagging health issue remains that I just
4 can't seem to deal with, and that's the periodic
5 episodes of gout. I was first diagnosed with gout
6 approximately 15 years ago when I had severe pain
7 in my foot, accompanied by significant swelling,
8 that woke me from a sound sleep. The pain was so
9 intense even the sheet covering my foot was painful
10 to the touch.

11 A visit the next morning to an emergency
12 clinic resulted in the diagnosis. With the
13 diagnosis in hand, treatment consisting of
14 colchicine tablets, allopurinol, a daily dose of
15 it, and a steroid dose pack, along with pain
16 relievers, the initial attack soon faded into a
17 distant memory. But my learning process began.

18 With this "rich man's disease," as the
19 physician called it, I was told to minimize all the
20 dietary items that were thought to bring on
21 attacks: red meat, red wine, et cetera. Despite
22 trying to comply with those restrictions, I had

1 subsequent attacks as bad as the first. And during
2 this period, I was trying to eat more healthy,
3 oatmeal in the morning, spinach salads, all the
4 healthy stuff, only to find out later that those
5 all contain purines, which also bring on the
6 attacks.

7 Then my kidney transplant eight years ago.
8 I thought everything would be fine after that, and
9 it was at first. My doctors reduced my allopurinol
10 to one tablet, 100 milligrams every other day. But
11 two years post-transplant, while on a cruise with
12 my donor cousin's family, I suffered another attack
13 and almost didn't remember what it felt like, and
14 it took me a while to remember. But with the
15 swelling continuing, I was forced to go to bed in
16 my cabin and reside there.

17 I had to inconvenience the ship's doctor
18 during the midnight buffet and miss many of the
19 last two days' cruise events due to the attack. I
20 thought my transplant would fix everything. As I
21 said, I'm an informed consumer. But I didn't
22 realize that my kidney function, while vastly

1 improved, is still impaired.

2 So I research issues. Discuss with my
3 physician regularly all my health issues. I see my
4 nephrologist regularly, have my bloods monitored,
5 including uric acid levels. We've discussed the
6 fact that with allopurinol and colchicine, they're
7 both toxic to my kidneys; actually, kidney. My PKD
8 kidneys have been removed. We've discussed
9 eliminating allopurinol entirely from my
10 requirement, but the problem is, if it's not
11 broken, don't try to fix it. So I'm still on my
12 daily or my every-other-day dose of allopurinol.

13 I've just become aware, as a result of being
14 invited to speak here today, that alternatives are
15 being considered. I would heartily endorse
16 providing alternative pharmaceutical treatments for
17 chronic kidney disease patients. Thank you for
18 your time and consideration.

19 **Committee Discussion**

20 DR. O'NEIL: Thank you, and thank you to all
21 the open public hearing speakers.

22 The open public hearing portion of this

1 meeting has now been concluded, and we will no
2 longer take comments from the audience. The
3 committee will now turn its attention to address
4 the task at hand -- actually, in a moment we
5 will -- the careful consideration of the data
6 before the committee, as well as the public
7 comments.

8 First we will begin with a brief response to
9 some of the questions raised during the earlier
10 sessions, and the sponsor will have about five
11 minutes to comment. Thank you.

12 DR. MUNDEL: Thank you, Dr. O'Neil. Trevor
13 Mundel.

14 I would hate the committee and this therapy
15 not to be available to patients because of a
16 misimpression that may have been created, and that
17 is around our intended use. And Dr. Mikuls had
18 this question.

19 So our intended use of this selective
20 treatment for gout is on demand. Patients who do
21 not respond to the first injection should not
22 receive it again, and we can label for that.

1 If I could have the slide up, A2.

2 So this is a slide which shows the
3 retreatment data, the first retreatment in green
4 and the second retreatment here in orange. In
5 addition to the initial acute pain treatment,
6 nonresponders not receiving subsequent treatments,
7 we also believe that patients over here who reflare
8 rapidly after the first treatment also represent a
9 different population and should not be retreated.
10 These are the treatment failures.

11 So I think what we have over here is a true
12 treatment on demand, not the kind of chronic
13 treatment that we have been talking about in the
14 background.

15 The other issue I wanted to raise was in
16 terms of the dose selection of our 150-milligram
17 dose and the prescription that we should not pay
18 attention to statistical significance in phase 2
19 studies because this may lead to the selection of
20 too high a dose.

21 I have a different view from the FDA on
22 that, particularly in the rheumatologic disorders,

1 and our experience has been that in phase 2, where
2 you have a very homogeneous population and you are
3 dealing with very selected investigators, you often
4 generate very large effect sizes which you actually
5 see go down in phase 3 with increased variability,
6 and you often lose statistical significance.

7 That was in fact the case over here, where
8 our 20-millimeter change in phase 2 dropped to
9 10 millimeters in the phase 3 for the 150, and we
10 now had patients who had recurrent flares, which we
11 didn't see in phase 2. Had we have selected the
12 90-milligram dose, we would actually not be here
13 today.

14 There was another discussion around the uric
15 acid levels.

16 If I could have the slide on our uric acid
17 level, 44. I think it's well-known to the panel
18 that in acute gout attacks, what one often sees is
19 uric acid levels that are either normal or
20 sometimes low. And this is ascribed to the
21 uricosuric effect of the inflammatory cytokines.

22 This data over here is data which comes not

1 from the acute attack situation, but it's from our
2 phase 2 study in which we studied patients who were
3 initiating uric acid-lowering therapy. And what
4 you can see over here is that in this circumstance,
5 when patients were dosed with canakinumab at a
6 variety of doses, in fact you see the uric acid
7 levels not rising but dropping.

8 So I think it is entirely anticipated that
9 there would be small changes in the uric acid
10 levels in the acute flare situation, which is
11 consistent with the known pathogenesis of those
12 small changes.

13 Actually, Dr. Edwards, if you'd like to
14 comment on that.

15 DR. EDWARDS: Larry Edwards. I just wanted
16 to correct a concept that got presented by the FDA,
17 and this is going to result in kind of a paradigm
18 shift like this committee had to face over the past
19 couple years, where you were looking at urate-
20 lowering drugs. And when gout flares occurred
21 after that, it was viewed as a bad thing. And then
22 we all come to understand that the more potent and

1 the more rapid those new agents were at lowering
2 uric acid, the more likely people were to flare.
3 So they were actually a monitor of increased
4 potency.

5 The same thing is true of the data that was
6 made with the uric acid levels at the time of the
7 acute flare. What's called an elevation in uric
8 acid related to the initiation of canakinumab is
9 not that at all. There is no data on what the
10 monosodium urate -- I'm sorry -- the serum urate
11 levels were prior to the initiation of the flare.

12 These first uric acid levels were obtained
13 1, 2, 3, 4, 5 days into the flare, when we all know
14 that uric acid levels are suppressed below their
15 baseline level because of the presence of IL-6.
16 What you're seeing with the initiation of
17 canakinumab is a rather remarkably quick reversal
18 of the inflammatory process that leads to this
19 initial uricosuria during the acute flare, and,
20 moreover, return to a baseline.

21 So I think that the concept that this is
22 elevating serum urate levels is not that. It's

1 simply allowing them to return to their baseline at
2 a more rapid rate, indicating that the inflammation
3 is under better control. Thank you.

4 DR. SHETZLINE: Then finally, the last point
5 is a follow-up to Dr. Suarez-Almazor on the 43
6 patients. We did a quick review of the data, and
7 the 43 patients in the table we showed on the
8 exposure-adjusted reporting rate, that represents
9 18 patients reporting 32 events. There were
10 9 patients reporting one event and 9 patients
11 reporting more than one event. Thank you.

12 DR. O'NEIL: Thank you.

13 We now have about 30 minutes to pursue
14 further questions, and there were a number of
15 panelists who had questions for both the sponsor
16 and for the FDA. I would like to start with
17 questions for the sponsor, and we'll give about 10
18 to 15 minutes to that, and then we'll follow with
19 questions to the FDA. And I would like to take the
20 chair's prerogative and ask the first question in
21 pursuit of the discussion on uric acid levels.

22 Is there any evidence, or in the early

1 studies, did the company look at uric acid
2 excretion in response to the agent? Is there
3 evidence that perhaps the fluctuations in uric acid
4 level indeed reflect changes at the local crystal
5 deposition level, leading to increased removal of
6 the uric acid perhaps because of changes in pH or
7 whatever, changes in the inflammatory milieu at the
8 uric acid crystal level? And do we know anything
9 about whether it increases or decreases uric acid
10 excretion?

11 DR. SHETZLINE: I'm sorry. We don't have
12 data on the effects on uric acid excretion. Sorry.

13 DR. O'NEIL: I like to stump the chumps.

14 [Laughter.]

15 DR. O'NEIL: The next question is from
16 Dr. Neogi.

17 DR. NEOGI: I have a couple of questions.
18 First, with regards to the efficacy of an IL-1
19 blockade, it would be anticipated that it would be
20 most efficacious given as quickly as possible. I
21 was wondering if the sponsors had data regarding
22 efficacy based on how quickly the participants were

1 enrolled, since they had a 1- to 5-day window for
2 being randomized.

3 DR. GATLIN: Yes. We do have that data, and
4 I will share that data with you that shows that
5 regardless of when patients were treated within the
6 5-day window specified per protocol, there was
7 consistent benefit in terms of pain reduction.

8 If I could have the slide up, please. Per-
9 protocol patients were instructed to report to the
10 investigator's office within five days of the onset
11 of their gouty arthritis attack. And what we have
12 here is we have divided the data looking at the
13 change in visual analog pain at baseline, 24 hours,
14 72 hours, and 7 days based on the time of treatment
15 after the beginning of the attack.

16 It's true that those patients who were
17 treated early had the most substantial benefit,
18 with a mean pain score of less than 10 at 7 days.
19 However, you will see that all of these patients
20 had significant pain at their baseline, and all of
21 them at every time point measured had a substantial
22 benefit in terms of pain reduction.

1 DR. NEOGI: The other question I had was
2 with regard to the comparator drug choice. And I
3 know, in the documents provided, there was an
4 argument made that triamcinolone 40 milligrams was
5 an appropriate drug dose, given that it's been used
6 in other regions. However, there's only been two
7 trials studying 60 milligrams of triamcinolone. I
8 was wondering if the sponsors could comment on that
9 comparator drug choice.

10 DR. GATLIN: Yes, we can. We do believe, as
11 we stated in our briefing book, that 40 milligrams
12 of triamcinolone was an appropriate comparator to
13 use in this program. As we stated before, we chose
14 not to use a placebo in this program, as this is a
15 very painful condition and we wanted to be able to
16 observe these patients over a prolonged period of
17 time to assess the efficacy of canakinumab in
18 treating their acute flare.

19 If I could have the slide up, please. And
20 this slide, if we look at the far right-hand
21 column, it has the efficacy of triamcinolone in
22 terms of pain reduction. And you can see at

1 72 hours, there was a good reduction of pain of
2 43 millimeters, albeit one that was significantly
3 smaller than that achieved with canakinumab 150.

4 Could I have the next slide up, please? And
5 also, about 54 percent of patients reported a good
6 or excellent response, again smaller than that with
7 150 milligrams of canakinumab.

8 So we believe that we've demonstrated that
9 in our hands, that the appropriate choice of
10 triamcinolone 40 milligrams was a reasonable choice
11 for a comparator. But furthermore -- if I could
12 have this slide up -- I'd like to just put into
13 context the efficacy that we've seen with
14 40 milligrams of triamcinolone.

15 Now, this is a slide that puts data from
16 different published studies on one slide, which of
17 course is something we don't often do. But I think
18 it's important to look at the efficacy of
19 triamcinolone here in yellow in terms of pain
20 reduction over time from our phase 2 program and
21 compare it with three different published studies
22 of indomethacin 50 milligrams t.i.d., which is a

1 robust NSAID for the treatment of the pain of gouty
2 arthritis, and you can see that it compares
3 favorably. So, therefore, I believe that the
4 40-milligram dose was an appropriate choice to use
5 as a comparator.

6 DR. NEOGI: A third question is with regard
7 again to the serum uric acid elevations. I
8 appreciate Dr. Edwards' slide that showed the data
9 from the prophylaxis studies. I was wondering if
10 there was any serum uric acid elevations in the RA
11 or CAPS populations.

12 DR. SHETZLINE: Yes, we do have data from
13 the RA program.

14 Could I have the slide up, please? This is
15 the rheumatoid arthritis study data out to
16 12 weeks, and these are serum uric acid levels.
17 This is in micromoles per liter, so you can use
18 your 60 conversion for milligrams per deciliter.

19 But roughly, this is the high dose that we
20 talked about, a 600-milligram IV loading dose, and
21 then 300 milligrams sub-q for 2 weeks in 71
22 patients, and then 300 milligrams every 2 weeks and

1 150 milligrams every 4 weeks compared to placebo.
2 And you can see virtually minimal effect on a serum
3 uric acid for the duration of the study monitored.

4 DR. NEOGI: And then one final question
5 regarding the safety of retreatment. I am still
6 having difficulty understanding how many total
7 number of participants had repeated flares versus
8 how many had repeated treatment. The reason I ask
9 is I imagine there may have been some adverse
10 events that precluded some people from being
11 retreated, and this goes back to that concept of
12 depletion of susceptibles, that the longer-term
13 safety may be more difficult to assess because
14 those that had an event did not go on to have
15 recurrent treatments.

16 DR. SHETZLINE: We had 118 patients who
17 received at least one additional retreatment, and
18 then we had 43 patients who had more than one
19 retreatment. In terms of the -- maybe I could see
20 the slide again? Yes.

21 In terms of breaking down for people who
22 could have been retreated and did not receive

1 retreatment, I don't know if we have that data
2 right now.

3 Oh, we have a disposition slide? Okay.

4 DR. GATLIN: So the per-protocol, when we
5 think about patients who were retreated, patients
6 who reflared early in that first 2-week interval
7 were not allowed to be retreated. So the first
8 group of patients we can talk about are patients
9 who had another attack within 14 days. There were
10 16 triamcinolone patients and 4 canakinumab
11 patients in the two phase 3 trials who had a new
12 attack in that early time period and were not
13 retreated.

14 If I could have slide A2, and go back to the
15 discussion of the frequency of retreatments. Could
16 I have the slide up, please? So again, this looks
17 at the first retreatment. And we'll pull up data
18 from the trial disposition. But again, this shows
19 that most retreatments have occurred at 6 to
20 12 months after the initial attack. There were
21 very few patients who were retreated early. And
22 again, as Dr. Mundel said, that those are

1 patients -- most of whom who do not respond, are
2 patients we would not recommend for repeated
3 treatments.

4 I don't believe we have an answer to your
5 specific question, which I understood was patients
6 who had a second attack but were not retreated due
7 to an adverse event.

8 Is that your question? We don't have an
9 answer to that specific question, but we are
10 looking for it.

11 DR. NEOGI: Thank you.

12 DR. O'NEIL: The next question is from
13 Ms. Aronson.

14 MS. ARONSON: I had listed when it was for
15 the FDA. Is it okay to ask that question now?

16 DR. O'NEIL: We'll put you at the top of
17 that next pile.

18 MS. ARONSON: Okay. But I have a quick
19 protocol question. The protocol question relates
20 to the very few incidences of injection site
21 responses, as far as allergic responses.

22 Within the protocol, was anything allowed

1 such as acetaminophen, or any other drug given that
2 may have mitigated any kind of reaction?

3 DR. GATLIN: So per protocol, we did allow
4 rescue medication for the treatment of the pain of
5 the acute gouty arthritis attack. If I could
6 have -- that's in injections.

7 Yes. So I'm going to speak to the rescue
8 medication that was allowed so you'll know what
9 people had on board; then we can speak to the
10 injections.

11 If I could have E96, I can share with you
12 the rescue medications that were allowed, and then
13 we can address your question about for injection
14 site reactions. 196, please.

15 So rescue medication was allowed in the
16 protocol within seven days of an injection. The
17 rescue medication was only to be administered after
18 the first 6-hour assessment of pain, and then was
19 to be withheld within 4 hours of the next pain
20 assessment. So patients could have taken one of
21 these medications within six hours of their
22 injection.

1 They were allowed to take acetaminophen, 500
2 milligrams, to a maximum of 1 gram per dose or
3 3 grams per day. They could also take codeine, to
4 a maximum of 180 milligrams per day. Or they could
5 take oral prednisone, 30 milligrams a day for 2
6 days, then to be down-titrated. So the possibility
7 did exist that within six hours of getting an
8 injection, some patients did receive acetaminophen,
9 codeine, or steroid.

10 DR. SHETZLINE: So in terms of the injection
11 site reaction question -- can I have the slide
12 up -- I can show you the events that happened.
13 These are the injection site reactions for our
14 phase 2 and our phase 3 programs. You can see the
15 injection sites reported and the reporting term,
16 pain, swelling, induration, redness, itching, or
17 hemorrhage.

18 As I mentioned in the core presentation,
19 there were two mild injection site reactions, or
20 two moderate and one mild injection site reactions,
21 reported as adverse events, but we don't have the
22 specific medications patients may have taken to

1 alleviate those symptoms.

2 DR. O'NEIL: The next question will be from
3 Dr. Fletcher.

4 DR. FLETCHER: Mine was for the FDA, so I'll
5 wait.

6 DR. O'NEIL: Next, Dr. -- I'm sorry,
7 Mr. Snarsky.

8 MR. SNARSKY: Can I make a comment now?
9 Okay.

10 As a person living with gout for about
11 10 years, I started out on losartan, which worked
12 really well. And then I lost my insurance, and I
13 went on to allopurinol, which I'm currently on.
14 It's working great. I've never had a flare up, no
15 problems.

16 My concern about this drug is the
17 affordability for people who don't have drug
18 coverage. Would the whole idea be to prevent
19 attacks as to treating an attack when you have it?
20 It sounds like here you have an attack, and you
21 have to run to the doctor like on a Saturday night
22 or a Sunday morning when there's no doctor to get

1 an injection; where if you're on a pill, something
2 that's constant, you don't have the flare ups, you
3 don't have the attacks, and you don't need to see
4 the doctor.

5 That's basically my comment. Thank you.

6 DR. SHETZLINE: Mike Shetzline. No, that's
7 a fair comment, especially with the nature of the
8 study design. So based on the targeted therapy
9 we've addressed and the reason we have the target
10 population we have, which is a select group of
11 frequently flaring patients, we believe that these
12 would be patients pre-identified by physicians who
13 would benefit from therapy. And hopefully that
14 could initiate preparations for the gouty arthritis
15 attacks to be treated with canakinumab.

16 So we would envision, because of the select
17 group of patients in need, that these would be
18 patients easily identified by physicians ahead of
19 time.

20 MR. SNARSKY: The side effects of this drug
21 really scares me. And I also have congestive heart
22 failure and coronary artery disease and a thyroid

1 problem, and it's scary. You know? I just --

2 DR. SHETZLINE: Maybe if I could comment on
3 this. From a cardiovascular perspective, we have
4 done a thorough review of our cardiovascular
5 safety. We have a cerebrum/cardiovascular event
6 review group who looks at all of the events that
7 are anywhere related to cardiovascular events, and
8 we've shown no increase in events. There were two
9 reports that made major adverse coronary event
10 classification in both canakinumab and
11 triamcinolone.

12 From a cardiovascular perspective, you
13 should also be aware that there is preclinical and
14 clinical evidence that supports a potential benefit
15 for canakinumab in cardiovascular disease. And
16 that's the study I alluded to earlier, where we're
17 doing a cardiovascular risk reduction study because
18 there is evidence that supports the fact, as
19 Dr. Mundel alluded to, that cholesterol crystals
20 behave in a similar way to monosodium urate
21 crystals to activate the inflammation that could
22 predispose patients to suffer coronary events,

1 myocardial infarctions.

2 Maybe Dr. Edwards can address the clinical
3 part.

4 DR. EDWARDS: Yes. I'm happy for you that
5 you're not suffering from frequent attacks. I
6 think that it's wonderful, and you're absolutely
7 right. The mainstay of all rheumatologists, of all
8 physicians, is to prevent flares and to treat the
9 disease, like yours has been, so that you don't
10 have flares. That's the goal in all of us, not to
11 intermittently treat the pain in perpetuity.

12 I think that were you to be having frequent
13 attacks, given the comorbidities that you have,
14 this would actually be a fairly good drug for you,
15 given the alternatives that you would need to be
16 taking, even though those were in pill form and you
17 might have them readily available at your house.

18 If there were other contraindications, if
19 you had found that you couldn't be taking those
20 because of worsening of your congestive failure or
21 worsening of your other problems, then this is an
22 option. And these are the very tip of gout

1 patients we're shooting for, where they have so
2 many comorbidities that the standard therapies just
3 aren't good.

4 DR. O'NEIL: I would just like to follow up
5 your question because no one has addressed what the
6 cost of this drug will be.

7 MR. KOWALSKI: Rob Kowalski, regulatory
8 affairs at Novartis. So we actually have not set
9 the price for the drug yet, but I can tell you that
10 Novartis has one of the most generous programs, if
11 you look across our entire portfolio, of supporting
12 patients, whether it's private-pay patients or
13 actually even public-pay patients, through
14 foundations and other mechanisms.

15 We have one of the most generous patient
16 assistance programs in the industry, including even
17 at the co-pay level. We've done that in areas of
18 multiple sclerosis. We've done it in areas of
19 asthma. And we will offer the same thing in this
20 area, regardless of what the price is. That is
21 something that we've already determined; this will
22 actually fall into the category of where we will be

1 offering significant availability to patients. We
2 want patients to be able to use the drug.

3 MR. SNARSKY: But Novartis took me off of
4 free support because I'm now getting Social
5 Security and I'm out of -- I'm making too much
6 money at \$9,000 a year, and they can't give me the
7 drug any more, whereas other drug companies are
8 supplying me with free drugs. I'm concerned about
9 the cost of this drug.

10 DR. O'NEIL: I think that does underscore
11 the importance of further exploring this.

12 The next questioner is Dr. Kerr.

13 DR. KERR: I was wondering, and you can
14 correct me if I'm wrong, is there PK variability
15 with age with this drug? I think I came across
16 something. And the reason I'm asking is that I
17 think the eldest patients you had in the study were
18 65. And I'm thinking that the patients who would
19 be intolerant or couldn't take NSAIDs or colchicine
20 are in fact older patients who would have more
21 comorbidity. And then I wouldn't have any data to
22 support not only the efficacy but, more importantly

1 the safety in that group.

2 DR. HOWARD: Dan Howard. I'm from
3 pharmacokinetics and pharmacodynamics. And thank
4 you for that question.

5 Slide up, please. I'm glad to say that
6 there is no correlation between clearance of the
7 drug and age. In fact, we looked across a number
8 of demographic variables. Age did not show up as
9 one that changed the clearance of the drug.

10 DR. O'NEIL: We have one more question for
11 the sponsor. Dr. Gibofsky?

12 DR. GIBOFSKY: We're told that 50 percent of
13 109 patients in 2356 were treated with urate-
14 lowering therapy and 29 percent of 99 patients in
15 study 2357 were treated with urate-lowering
16 therapy. So that's about 86 to 88 patients who
17 were treated with urate-lowering therapy.

18 The statement is made in the briefing book
19 that clinical data show that canakinumab can be
20 safely administered with urate-lowering therapies.
21 And I'm just wondering, were all those patients on
22 xanthine oxidase reducing therapies? Can you break

1 them down by allopurinol versus, say, febuxostat?
2 Were any patients on any therapies other than
3 urate-lowering therapies? And what do we know
4 about interactions with other than urate-lowering
5 therapies? Which are now currently available to be
6 used.

7 DR. GATLIN: Gatlin, Novartis. I can
8 address what urate-lowering therapies the patients
9 were on. And in our program, the vast majority of
10 patients who were on urate-lowering therapy were
11 taking allopurinol. We had about 3 patients who
12 were randomized to canakinumab who were on
13 febuxostat. And there were no patients taking
14 probenecid, and pegloticase was not approved at
15 that time.

16 Dr. Howard will address the drug/drug
17 interaction question.

18 DR. HOWARD: The drug has a very low
19 potential for interaction with other small
20 molecules, and that's primarily because the drug is
21 metabolized through proteolytic catabolism while
22 other small molecules go through the liver.

1 DR. GIBOFSKY: But then it's still fair to
2 say that at this point we can only talk about the
3 lack of interactions with the xanthine oxidase, and
4 in particular, allopurinol, with only three
5 patients having received febuxostat and none having
6 received pegloticase. So that statement would need
7 to be modified.

8 DR. GATLIN: That's correct.

9 DR. O'NEIL: We would now like to pose a few
10 questions further to the FDA. The first questioner
11 is Ms. Aronson.

12 MS. ARONSON: I have a question about
13 potential malignancy. In the FDA briefing
14 document, it was noted that the IL-1 β is known to
15 modulate estrogen, and uterine tumors are known to
16 occur from endocrine disturbances.

17 I'm wondering about post-menopausal women
18 and whether there should be something noted about a
19 potential problem in this group because there was a
20 small number of women in this study, but yet the RA
21 study had more women because of incidence. But
22 there were more malignancies in the RA study.

1 So is there any caution regarding the
2 endocrine disturbances, the potential?

3 DR. LAPTEVA: First of all, the briefing
4 document that you're talking about may not be the
5 FDA briefing document about the endocrine tumors.

6 So there was no clinical data on endocrine
7 tumors. There could have been some preclinical
8 data. Yet on the clinical data that was submitted
9 in this application, we can't really tell whether
10 there was any increased risk because there were
11 only two tumors in the canakinumab gout program.
12 But yet, on the other hand, the duration of
13 observation was very short, so you won't
14 necessarily see something that would be of an
15 increased risk for malignancy.

16 In general, biological therapies that have
17 immunomodulating effects are known to somehow
18 interfere with immunosurveillance of malignant
19 cells, and that's how the current views on how the
20 malignancy risk could potentially be increased with
21 these therapies.

22 We did not see much on the canakinumab and

1 gout population. We did see some tumors in the
2 rheumatoid arthritis program with longer duration
3 of therapy, where people were getting the drug
4 every two weeks. But the data were too limited to
5 actually put any number on the risk of malignancy
6 there because even in the rheumatoid arthritis
7 program, there were a few malignancies.

8 The sponsor, if they would like to add
9 something?

10 DR. SHETZLINE: No. I think that's correct.
11 We saw, as I presented, two malignancies in the
12 phase 3 program -- I mean, in the phase 2/3
13 program -- one in a canakinumab-treated at greater
14 than 200 milligrams, and one on colchicine. So
15 they were balanced in that duration study.

16 We saw eight malignancies in total in the RA
17 program. And as I presented -- you can put the
18 slide up -- we didn't see any evidence of increased
19 reporting of malignancies with the further duration
20 of exposure in the RA program. But nonetheless,
21 there were eight events reported. They were
22 primarily reported early.

1 So there doesn't appear to be a chronicity
2 in terms of increased reporting, but the numbers
3 are low. Our current label for CAPS does include a
4 warning to physicians in a setting that
5 immunosuppression can be related to malignancies,
6 and they should be aware of that.

7 Oh, and we are actually, as I also alluded
8 to, pursuing a long-term registry program. It's a
9 proposal to the agency in terms of being able to
10 monitor things and specifically related to aspects
11 around malignancy.

12 DR. O'NEIL: If I could just ask a question
13 of Ms. Aronson. I thought your question was not so
14 much directed at the risk of malignancy alone, but
15 rather the statement that was indeed in the FDA
16 briefing document in the preclinical studies --

17 MS. ARONSON: It was in the preclinical
18 section.

19 DR. O'NEIL: -- regarding one marmoset
20 uterine cancer, that the drug is known to interact
21 with estrogen. And therefore she was asking, I
22 think, if indeed such an interaction with estrogen

1 might indeed be an issue in the postmenopausal
2 female patient who may or may not be taking HRT.

3 DR. LAPTEVA: Right. We are not aware of
4 any mechanistic plausible explanation on what can
5 happen there. There were some preclinical
6 observations, but there was nothing seen in the
7 clinical program.

8 DR. O'NEIL: The next question is from
9 Dr. Mikuls.

10 DR. MIKULS: This is a somewhat
11 philosophical question. I was debating who to ask,
12 but FDA is stuck with it.

13 I'm curious about the indication. It was
14 clear in the briefing document that the second part
15 of that indication was new and novel. And I'm
16 wondering if the FDA has concerns in regards to
17 that indication in terms of what the implications
18 of that might be.

19 So there is a suggestion in that second
20 statement about extending the time to the second
21 attack, that it is indeed a preventive therapy. I
22 don't think that's a stretch to say it might be

1 misinterpreted that way. I'm not at all suggesting
2 that the sponsor is trying to be misleading. But
3 that indication, it's disappointing. Thirty
4 percent of patients in these studies are on urate-
5 lowering therapies. These are severe gout
6 patients; again, speaking -- perhaps suboptimal
7 care for many of our gout patients.

8 I have some concern that that kind of
9 indication could inappropriately lead to
10 undertreatment with urate-lowering therapy, which I
11 think many of the experts understand the vital
12 nature of. So I'm wondering how you're getting
13 your arms around that indication.

14 DR. OKADA-YIM: Yes. Well, that's why
15 you'll see some of the questions that are being
16 posed to the committee really do break up the
17 indication by the acute treatment indication versus
18 that sort of tagalong claim in the indication
19 statement. We also have concerns about that and
20 would love to hear your opinion regarding whether
21 it's going to get misinterpreted or not.

22 DR. MIKULS: You can tell by the way I asked

1 the question I do have that concern. Yes.

2 DR. O'NEIL: Dr. Fletcher?

3 DR. FLETCHER: Yes. Thank you.

4 My question is to Dr. Okada. In the early
5 discussion about the phase 2 program and "change in
6 philosophy" over time, I'm curious about when and
7 if FDA communicated that kind of change to the
8 sponsor and in what time frame relative to the
9 start of the phase 3 program or during the phase 3
10 program that would allow them an opportunity to be
11 aware of your concern in that way, given the safety
12 findings and other things here are certainly in the
13 label.

14 I realize it's a different patient
15 population and so forth. But I think the committee
16 ought to be aware of the FDA's thinking on that,
17 and timing.

18 DR. OKADA-YIM: Yes. So, as you know, we
19 joined a different division. We joined the
20 pulmonary/ allergy division last year. And at that
21 point, the horse was pretty much out of the barn.
22 When the sponsor came in for a pre-sBLA meeting, it

1 was already a done deal. And, really, we hadn't
2 had an opportunity to examine the data in detail at
3 that point.

4 So as we did at phase 2, without having any
5 idea of what the safety data would show, we didn't
6 have a major objection to the 150-milligram dose.
7 It's an approved dose. It's just a question of
8 whether the risk/benefit profile would be
9 appropriate in this particular population, and
10 that's what we didn't have access to before the
11 actual sBLA was submitted.

12 DR. FLETCHER: But you're generally aware of
13 the size of the safety database that probably would
14 be provided, given your agreement, or FDA's
15 agreement, at least on the phase 3 program and at
16 the end of phase 2? Would you comment on that?
17 The size of the safety database, was that different
18 than what you expected?

19 DR. OKADA-YIM: I wouldn't say that we got a
20 different size of a safety database than what we
21 expected. It is generally considered to be being
22 proposed for an acute treatment, in which case we

1 don't really apply the same chronic treatment
2 standards.

3 Where this kind of crosses the line a little
4 bit and which makes the discussion
5 complicated -- pardon me, Dr. Carome, but it's
6 somewhat complicated -- is that the pharmacodynamic
7 effects of this molecule really are extended. And
8 tagging on the extra claim sort of makes it sound
9 like maybe it should be used for preventing flares.
10 So I believe that those do complicate the
11 risk/benefit assessment, and that's why we're
12 discussing it today.

13 DR. FLETCHER: Thank you. I appreciate it.

14 DR. O'NEIL: This is turning into an
15 elephant with no end in that the committee is
16 coming up with increasing numbers of questions.

17 Very, very quickly, Dr. Buckley, followed by
18 Dr. Peduzzi, and then I think Dr. Felson, unless he
19 decides he doesn't want to ask it.

20 DR. BUCKLEY: So I think the next steps will
21 be for us to look at benefits and risk. And
22 sometimes a thing that helps me think that through

1 is what I would say to a patient as I discuss those
2 risks and benefits.

3 I don't know if you've looked at number
4 needed to treat to have a serious adverse event.
5 Back of the envelope, I think if I was going to
6 talk to a patient about taking this drug, I might
7 say, you've got about a 90 percent chance of a
8 response. In terms of infection, you have maybe
9 almost a 20 percent chance of having some
10 infection, but only 1 in 50 chance of having a
11 serious infection; but that risk will extend for
12 months after I treat you. And that's if you're
13 generally fairly healthy.

14 I think what I'd have to say to a patient
15 with significant renal disease or other infection
16 risks, even a transplant patient who's on
17 immunosuppression, as I have no idea -- in fact,
18 the transplant patient might not be a candidate.
19 So if we go back to someone with significant renal
20 disease, I'd probably have to say, from this data,
21 I don't know for sure what the risks are.

22 Is that a fair summary, or would you

1 describe these risks in a different way to a
2 patient?

3 DR. OKADA-YIM: No. I think the way you're
4 describing it makes sense. We actually, I don't
5 think, have the number needed to treat
6 calculations. I don't know if the sponsor has
7 anything in that regard. But that's a very good
8 point. I think on a patient-by-patient level, one
9 needs to make that sort of cutoff.

10 I think what we were hoping for was having a
11 very, very clear population to benefit in which
12 even these small risks of serious infections would
13 be justifiable, such as the renal failure
14 population you were talking about, and we instead
15 got all comers, pretty much.

16 DR. SHETZLINE: Yes. Madam Chair, if you
17 want us to comment on the NNT and the NNH, we can
18 do that, if you'd prefer.

19 DR. O'NEIL: Sure, very quickly.

20 DR. SHETZLINE: Slide up. We did actually
21 calculate the NNT and the NNH. You can see on this
22 slide, the NNT, in this case, it's calculated

1 relative to triamcinolone. And I think one of the
2 things we've talked about at length this morning is
3 how efficacious triamcinolone was. So even in the
4 setting of a good efficacious comparator, the
5 number needed to treat beyond the benefit of
6 triamcinolone would be 5.7 on our primary endpoint,
7 which is 50 percent pain reduction at 72 hours.

8 You can see other calculations based on a
9 major clinical benefit, which includes the aspect
10 of no new flare in the 12-week period, and then
11 also no new flare within a 24-week period. We
12 decided to call those a major clinical benefit.
13 And then finally, no new attack in 12 weeks, it
14 prevents one attack, 3.1; or no new attack in
15 24 weeks at 2.2.

16 That means the number of patients the
17 physician would have to treat in order to have a
18 successful outcome. And the successful outcome in
19 this case would be no new attack at 24 weeks
20 prevents one flare. So that's the number needed to
21 treat.

22 The next slide, please? Then we've also

1 done it for the harm, the NNH. And this again is
2 compared to triamcinolone. And if you take all
3 SAEs, or any serious adverse effect, the number
4 needed to harm would be 25; so 25 patients in order
5 to harm one. If we look at infectious SAEs, the
6 number needed to harm would be 62.5, treating 62.5
7 patients to have an infectious SAE.

8 DR. O'NEIL: Thank you.

9 Dr. Peduzzi?

10 DR. PEDUZZI: I just had a point of
11 clarification about the indication. It seems to be
12 based on a secondary analysis, to reduce the
13 frequency of subsequent attacks instead of the
14 primary endpoint, which was pain intensity at
15 72 hours.

16 Why was the primary left out of that? Maybe
17 that's not a question for you. It might be a
18 question for the company. I just found it a little
19 bit confusing. You had two co-primary endpoints,
20 and they both weren't used to define the
21 indication, the proposed indication. Maybe I'm
22 missing something.

1 DR. LAPTEVA: Well, the best guess here
2 would be that the treatment of acute attack would
3 stand for the changes on the visual analog scale,
4 where there is an improvement in pain intensity in
5 patients who are experiencing acute attack.

6 DR. PEDUZZI: Then I would have expected
7 reduction in frequency of subsequent attacks to
8 have been a primary or secondary endpoint. It's
9 not even listed as a secondary endpoint in the
10 document that I saw, the briefing document. I just
11 found it a little bit odd.

12 DR. LAPTEVA: Since the sponsor proposed the
13 indication, they might want to comment on that.

14 DR. SHETZLINE: If we could have one slide
15 up, we'll just show the indication statement. The
16 primary, first part of the indication statement, we
17 had co-primary endpoints, two primary endpoints, in
18 the phase 3 program. The first part addresses the
19 pain reduction, so it's the acute benefit to
20 provide relief for the pain. And then the other
21 co-primary endpoint was related to delay to the
22 next flare. That's the second part of the

1 indication statement.

2 So, again, it was a much more challenging
3 endpoint to hit because it was a co-primary
4 endpoint. But both of them were part of our
5 program.

6 DR. O'NEIL: Dr. Felson?

7 DR. FELSON: Well, Dr. Peduzzi took one of
8 my questions, which I appreciate. Let me ask you a
9 point of information. This is a supplemental BLA.
10 Are there some rules and regs regarding this that
11 are different somehow from the approval of any
12 biologic or drug? Are there things we should know
13 in thinking about how we vote that relate to the
14 regulations regarding this? I've never seen a
15 supplemental BLA before.

16 DR. LAPTEVA: Well, the reason that you've
17 probably never seen a supplemental BLA before,
18 because usually the drugs that we take to advisory
19 committees would be new drugs, new molecular
20 entities, new drugs that are submitted under new
21 drug applications or new biologic license
22 applications.

1 This is not still an unheard-of situation,
2 where there could be a drug that is already
3 approved, but when there is an expansion on patient
4 population and different considerations for the
5 risk/benefit profile, the drug would need to be
6 discussed at the advisory committee meeting.

7 In terms of the regulatory submissions and
8 how we look at the drugs, usually, whether it's a
9 new drug or a supplemental BLA, they come in on the
10 standard clock, which is 10 months, or on the
11 priority clock, which is 6 months, and that usually
12 depends on certain characteristics of the
13 application. This one was not necessarily a
14 priority for any unmet need. It was a voucher that
15 the sponsor was redeeming, and Dr. Yim could
16 probably speak about it.

17 DR. CHOWDHURY: I'm Dr. Chowdhury. Maybe I
18 can take your question.

19 As far as assessment of efficacy and safety
20 goes for a disease, which we're discussing here,
21 the standards are the same whether it is a new drug
22 application, new biologic application, or

1 supplement. Now, what makes the difference between
2 a new application, which is a supplement, is that
3 the new application is the first time a biologic or
4 a drug is being discussed for potential marketing
5 in the U.S. In that context, there may have been
6 information other than safety and efficacy which is
7 important, for example, drug quality. With the
8 supplement, the product is already approved in the
9 market, so that aspect is addressed.

10 So there are other issues which go in the
11 new drug application which is not necessarily there
12 in the supplement. But for the purpose of this
13 discussion, which is purely efficacy and safety for
14 indication, the standards are the same.

15 **Questions to the Committee**

16 DR. O'NEIL: Thank you.

17 We will now proceed with the questions to
18 the committee and panel discussions. I would like
19 to remind public observers at this meeting that
20 while this meeting is open for public observation,
21 public attendees may not participate except at the
22 specific request of the panel.

1 For the voting questions, we will use the
2 electronic voting system for this meeting. Each of
3 you have three voting buttons on your microphone,
4 yes, no, and abstain. Once we begin the vote,
5 please press the button that corresponds to your
6 vote. The vote will then be displayed on the
7 screen. I will read the vote from the screen into
8 the record.

9 Next, we will go around the room, and each
10 individual who voted will state their name and
11 their vote into the record. You can also state the
12 reason why you voted as you did if you wish to.

13 We will now have the charge to the committee
14 by Dr. Yim.

15 **Charge to the Committee**

16 DR. OKADA-YIM: Okay. Sorry. I know you're
17 chomping at the bit to get to the questions. I
18 just wanted to give a quick overview of the
19 regulatory framework for this discussion.

20 As you've heard, FDA is asking the committee
21 to discuss the risk/benefit considerations of
22 canakinumab for the proposed indication and patient

1 population in gout. Some of the issues highlighted
2 include canakinumab's extended effects after a
3 single injection, the question of symptomatic
4 benefit versus increased risk of serious infections
5 and undesirable laboratory abnormalities, the fact
6 that the patient population may not really be
7 refractory, and that we only have one dose to
8 choose from.

9 To frame the discussion, just a quick
10 reminder of the governing regulations. FDA's
11 decision to approve depends on the determination
12 that the drug meets the statutory standards for
13 safety and effectiveness, manufacturing and
14 controls, and labeling.

15 In the questions that follow, you'll have
16 the opportunity to vote on the adequacy of the
17 efficacy and safety data separately, but for voting
18 questions 6 and 7 regarding approval for the
19 proposed indications, your vote should reflect your
20 assessment of both efficacy and safety together for
21 the proposed indications. The efficacy standard
22 describes the need for substantial evidence from

1 adequate and well-controlled investigations to
2 support the language proposed in labeling.

3 There are a number of safety reasons that
4 can underlie a refusal to approve an application
5 summarized here. These could include a lack of
6 adequate tests to document safety; that results
7 show the product is outright unsafe; or that
8 results simply do not show that the product is safe
9 for the proposed use; or, finally, that there is
10 insufficient information to determine whether the
11 product is safe for its proposed use.

12 Now I'll briefly describe the questions to
13 the committee that you'll be discussing here
14 shortly.

15 Question 1 is a discussion question
16 regarding the efficacy data in the application. In
17 particular, FDA is asking your opinion regarding
18 the dose-ranging data, whether the proposed regimen
19 represents acute treatment or more chronic
20 treatment based on what we know about the molecule
21 and the patient population and whether the data are
22 adequate to determine what the risk/benefit of the

1 product might be like over time with recurrent
2 treatment.

3 Question 2 is a discussion question
4 regarding the safety profile of the product.
5 Specifically, FDA asks for your review regarding
6 the safety signals mentioned and what you think the
7 potential risks would be of using canakinumab for
8 gout on an acute recurrent basis.

9 Question 3 is a voting and discussion
10 question regarding whether canakinumab at a dose of
11 150 milligrams has demonstrated adequate evidence
12 of efficacy for the acute indication of treatment
13 of gouty arthritis attacks in patients who cannot
14 obtain adequate response with NSAIDs or colchicine.

15 Question 4 is a voting and discussion
16 question regarding, again, the efficacy of
17 canakinumab, but for the additional claims of
18 extending the time to next attack and reducing the
19 frequency of subsequent attacks.

20 Question 5 is a voting and discussion
21 question regarding the safety profile of
22 canakinumab at 150 milligrams subcutaneously and

1 whether the safety profile is sufficient to support
2 its approval for use as an acute recurrent
3 treatment in the population of gout patients who
4 cannot obtain adequate response with NSAIDs or
5 colchicine.

6 Question 6 is a summative voting question on
7 whether you think that efficacy and safety of
8 canakinumab together are adequate to support
9 approval of the 150-milligram dose for the acute
10 indication of treatment of gouty arthritis attacks
11 in patients who cannot obtain adequate response
12 with NSAIDs or colchicine.

13 Finally, question 7 is a summative voting
14 question on whether you think the efficacy and
15 safety data together are adequate to support
16 approval of the 150-milligram dose for the
17 additional claim of extending the time to next
18 attack and reducing the frequency of subsequent
19 attacks. FDA greatly appreciates the committee's
20 consideration of these important issues.

21 With that, I'll turn the meeting back to
22 you, Dr. O'Neil.

1 DR. O'NEIL: Thank you.

2 Now we will proceed to the questions. The
3 first question is to discuss the efficacy data of
4 canakinumab, considering, A, the dose-ranging data
5 and whether doses lower than 150 milligram should
6 be explored further.

7 Why don't we start there, and then we'll
8 proceed to the others.

9 Dr. Suarez-Almazor?

10 DR. SUAREZ-ALMAZOR: Yes. Before we start
11 the discussion, may I ask a question related to the
12 phrasing of the indication, which are the
13 questions -- I mean, it's starting question 3.

14 But the way it's phrased where it says,
15 "patients who cannot obtain adequate response with
16 nonsteroidal anti-inflammatory drugs or
17 colchicine," given that we do not define refractory
18 gouty arthritis or number of attacks or anything
19 like that, would that mean that an approval would
20 be -- if one patient has one gouty attack just once
21 and does not respond to colchicine, this drug would
22 be approved for that patient in the longer term?

1 Is that the implication of this statement on
2 the indication?

3 DR. OKADA-YIM: I think the implication is
4 really sort of subjective. I do think the sponsor
5 is intending it to mean patients would have failed
6 at least one of the treatments, but how do you
7 define "fail"? We're not going to define that in
8 the label, necessary. So it is open to
9 interpretation.

10 DR. SHETZLINE: Madam Chair, may I clarify?

11 From the sponsor's perspective, we're
12 looking at the frequently flaring population, those
13 who have greater than three flares per year, and
14 that was directly what we studied within phase 3.
15 So the answer to your question is it would not be
16 for somebody who had the first new attack. That's
17 not who we're trying to treat with this product.

18 DR. SUAREZ-ALMAZOR: Yes. But it's knowing
19 the indication as we are getting ready to discuss.

20 DR. SHETZLINE: We would certainly be
21 willing to discuss that with the agency, yes.

22 DR. O'NEIL: All right. Who would like to

1 begin this discussion regarding the dose-ranging
2 data and whether doses lower than 150 milligrams
3 should be explored further? Good. Dr. Mikuls?

4 DR. MIKULS: So I found the data, albeit
5 small numbers -- the data between the 90 milligram
6 and 150 milligram as relatively compelling. I
7 mean, I think that there was clearly a difference
8 there in terms of pain response with the 150-
9 milligram dose. So if you're going to talk about
10 lower doses, you're going to be talking about
11 incrementally different doses, 120, 130, 140, where
12 you're really sort of really splicing it apart.

13 It's an interesting question, though,
14 because I think for the second -- this is where I
15 was getting at earlier with my question. For the
16 second half of the indication, it's a whole
17 different ball game because as I looked at the
18 briefing document -- and maybe I looked at it
19 wrong, but as I looked at it, it looked like lower
20 doses in a study we didn't talk a lot about today,
21 but in the prophylaxis study, lower doses
22 potentially had similar effects as larger doses.

1 So this is really hard because you're tying
2 together two things that in some ways in my mind
3 don't necessarily belong together. But if you
4 forced me to answer this question now, I would say
5 I don't know that there's a lot of benefit, in my
6 view, for acute treatment, one-time treatment, of
7 trying to splice through these variously smaller
8 doses. I don't quite get that.

9 DR. O'NEIL: Dr. Gibofsky?

10 DR. GIBOFSKY: I would concur with
11 Dr. Mikuls. I think the data at 150 is
12 sufficiently robust to demonstrate efficacy, and
13 the differential between 90 and 150 is not that
14 much to make a significant difference to justify
15 going to a lower dose. I think the importance of
16 getting the pain under control rapidly is a
17 significant factor.

18 I do agree with concerns about the second
19 half of the equation, which we'll get to in a
20 little while, but I think the efficacy data is
21 demonstrated.

22 DR. O'NEIL: Why don't we go quickly around

1 the room and just state comments about whether you
2 feel that efficacy at 150 is sufficiently
3 demonstrated.

4 Dr. Fletcher?

5 DR. FLETCHER: Yes, I do.

6 DR. PEDUZZI: I agree.

7 DR. FELSON: Yes. I thought the difference
8 between 150 and lower doses was substantial, and I
9 thought that was reasonable.

10 DR. NEOGI: I agree.

11 DR. GIBOFSKY: Noted.

12 MR. SNARSKY: I agree.

13 MS. ARONSON: I'm confused. I thought that
14 the sponsor suggested that lower doses weren't
15 efficacious. I'm just confused.

16 DR. SUAREZ-ALMAZOR: Yes. I agree. I think
17 150 is fine.

18 DR. BUCKLEY: I agree.

19 DR. O'NEIL: I also agree.

20 DR. MIKULS: I agree with myself.

21 DR. BLUMENTHAL: The 90-milligram dose is
22 really not very efficacious. So if we are to use

1 this drug, I think it should be used at the
2 150-milligram dose.

3 DR. KERR: Agreed.

4 DR. O'NEIL: The next part of the question
5 is whether the proposed regimen, 150 milligrams
6 with retreatment on demand, represents acute
7 treatment or a more chronic treatment.

8 The first person to comment on this is,
9 Dr. Blumenthal, who's been quiet.

10 DR. BLUMENTHAL: Well, I think one of the
11 things we're going to be discussing when we get to
12 indications is all the issues you get into with the
13 long half-life of the drug. We're going to talk
14 about indications in a minute, but I think
15 Dr. Suarez was correct that the real target group
16 for this drug is the patients who should not
17 receive nonsteroidals.

18 I think that's why the sponsor had to phrase
19 the indication the way they did. "Cannot receive
20 nonsteroidals" means either that they failed or the
21 physician feels that they should not be used. And
22 "cannot," I think would cover both of those

1 circumstances, so that's probably a reasonable way
2 to phrase it.

3 But I think the real target group is people
4 who should not receive nonsteroidals, should not
5 receive colchicine, and should not receive
6 corticosteroids. Anybody who would be better with
7 a 7-day course of corticosteroids without a lot of
8 harm, I'm struggling to see the advantage of a drug
9 with such a long half-life.

10 Now, there are some patients where there is
11 absolutely an advantage, a patient who has been
12 flaring, or is anticipated to flare, at a rate of
13 once per month. And if you have to use the regimen
14 of prednisone that Dr. Edwards was describing
15 earlier -- which is accurate, 35 milligrams a day
16 of prednisone for 4 consecutive days, tapered
17 gradually over a period of 2 to 3 weeks, is what is
18 often done in our most severe gout patients -- then
19 they end up with a frequency rate of once per
20 month. They end up spending most of the next two
21 to three months on prednisone, which is
22 immunosuppressive. So the immunosuppressive

1 effects of the monoclonal antibody actually start
2 to become an advantage rather than a disadvantage.

3 But it's really only in that group of
4 patients that two months of continuous
5 immunosuppression might be an advantage because
6 they're going to get that from your prednisone or
7 other therapy anyway. So in a patient who would
8 get better rapidly, I'm not sure it's an advantage
9 to have a drug with such a long half-life.

10 So when you start using a drug with such a
11 long half-life repeatedly, I think it does evolve
12 into a chronic immunosuppressive therapy for an
13 indication that doesn't require that very often.
14 There are absolutely patients who do, but they're a
15 relatively small segment of our patient population.

16 DR. O'NEIL: Dr. Suarez-Almazor?

17 DR. SUAREZ-ALMAZOR: Yes. And if I
18 understand the data correctly also, for those who
19 are taking urate-lowering agents, there was no
20 significant difference in time to flare or in
21 attacks between the two groups in the trials; is
22 that correct? For those who were on a baseline

1 urate-lowering regime.

2 DR. LAPTEVA: That's correct.

3 DR. O'NEIL: Dr. Fletcher?

4 DR. FLETCHER: I agree with Dr. Blumenthal.

5 But I do want to point out that the sponsor has
6 indicated that they're really focusing on just that
7 patient population that has very frequent flares
8 going in. And that probably is going to be part of
9 a discussion of what the label will actually look
10 like to inform and be sure that prescribers and
11 patients understand what this drug is really for.

12 DR. O'NEIL: Other comments to this issue?
13 Dr. Neogi?

14 DR. NEOGI: One way we can think about it is
15 with colchicine, which has an indication for acute
16 treatment but we use it differently for longer-term
17 chronic treatment -- I think the difficulty here is
18 that a single 150 dose doesn't allow us to play
19 around with a lower dose for that more chronic
20 treatment. And I'm still struggling with the two
21 different aspects of how this drug may be used.

22 DR. O'NEIL: Any other questions or

1 comments?

2 [No response.]

3 The third part of this question is that we
4 are asked to comment on the limited information
5 regarding repeat dosing and whether additional data
6 on repeat dosing over time should be obtained,
7 particularly in light of the intended population of
8 patients who may be at risk for more frequent
9 flares, patients in the studies had an average of 6
10 to 7 flares in the previous year.

11 Dr. Gibofsky?

12 DR. GIBOFSKY: Yes, there is limited
13 information regarding repeat dosing, and, yes,
14 additional data on repeat dosing over time should
15 be obtained. I believe we heard plans for a
16 registry of patients who receive this drug. I have
17 no doubt that studies would be undertaken to
18 collect that data anyway.

19 So we should obtain that data at some point
20 in time because I think it will be important to
21 understanding the use of an acute drug in a chronic
22 condition.

1 DR. O'NEIL: I did have questions as to
2 whether -- this is me commenting, not moderating.
3 I had questions about whether a 1-year registry
4 will provide sufficient data to really tell us. I
5 think a second and third year will be extremely
6 important. And although that may be derived in a
7 very extensively overlapping clinical population,
8 the individuals who have cardiovascular disease
9 from that longer-term trial that is planned, and
10 much larger trial, I think that the registry would
11 need to be more than one year.

12 Any other comments, folks? Does that
13 suffice for commentary?

14 [No response.]

15 DR. O'NEIL: The next question, question 2,
16 we are asked to discuss the overall safety profile
17 of canakinumab for gout, considering the
18 following -- I'm sorry. Let me first summarize our
19 responses to question 1.

20 With regard to the first question, we did
21 seem to have concurrence that there are big
22 differences in efficacy between the 90- and

1 150-milligram dose based on, granted, relatively
2 small numbers of patients treated at the lower
3 doses, but that the panel seemed to concur with the
4 sponsor that the 150-milligram dose did look
5 significantly more efficacious.

6 Regarding the proposed regimen, whether it
7 represented acute or chronic treatment, the niche
8 for this drug appears to be for the folks who would
9 need relatively more chronic treatment, it sounds
10 like, the people who have more recurrent disease;
11 and so that in some ways the chronic therapy may
12 not be inappropriate. But for individuals who have
13 less frequent flares or shorter flares, that this
14 drug does have a chronic profile in its
15 pharmacokinetics and its immunologic effects that
16 may be even longer than its pharmacokinetics; and
17 that this drug may be inappropriate for those who
18 don't need more frequent treatment.

19 Then regarding the third, there is indeed
20 limited information on repeat dosing and further
21 information is needed, but that the registry may
22 need to be longer-lived than proposed by the

1 sponsor.

2 The second question, now, is to discuss the
3 overall safety profile of canakinumab for gout,
4 considering the following: a) the safety signals
5 of infections, increase in uric acid level, decline
6 in renal function, and hypertriglyceridemia; and
7 b) the potential risk of using the drug in gout on
8 acute recurrent basis.

9 Dr. Neogi?

10 DR. NEOGI: With regards to infection, as
11 has been said repeatedly, we expect some increased
12 risk of infection with a biologic, such as anti-
13 IL-1 therapy. And then, as Dr. Blumenthal is
14 reviewing, for patients who have recurrent flares
15 who can't or don't respond to NSAIDs or colchicine
16 and were using recurrent courses of
17 corticosteroids, particularly for oral
18 corticosteroids, we know that there is a long-term
19 risk of infection even at low-ish doses of
20 prednisone intermittently given over years.

21 So although we can't compare that data in
22 this trial, I think we need to bear this in mind,

1 that that's the patient population we need to think
2 about in terms of the infection signal.

3 With regards to the increase in uric acid
4 level, it was reassuring that it was not
5 accompanied by increased flares and reassuring
6 that, in other settings, such as the prophylaxis
7 setting or RA, that there was no increase in uric
8 acid, and, therefore it may be a reflection of the
9 acute flare setting.

10 The hypertriglyceridemia, maybe someone on
11 the panel or the sponsors may be able to comment.
12 If I remember correctly, the anti-IL-6 therapies
13 were also accompanied by hypertriglyceridemia. And
14 I was wondering if, therefore, the uric acid and
15 hypertriglyceridemia may be in part related to
16 effects on IL-6.

17 I concur with Dr. Buckley that in the
18 patient population that we would likely be using
19 this, the patients with decreased renal
20 functioning, I think the decline in renal function
21 in this population is a bit of a concern and would
22 warrant further follow-up in a more severe renally

1 impaired population.

2 DR. O'NEIL: Dr. Felson?

3 DR. FELSON: Yes. I guess this is where I
4 maybe part company with Tuhina, my colleague. I
5 found the safety issues to be overwhelmingly
6 concerning. I found them especially concerning
7 because the people in this trial were not
8 necessarily the most severe gout patients that
9 would need this therapy. A lot of them, in my
10 experience, are older than many patients in this
11 trial, often with other comorbidities and renal
12 dysfunction, often at high risk of infection,
13 perhaps as high or higher than our RA patients.

14 I guess I learned as a fellow that you don't
15 go -- when I was debating whether to treat my gout
16 patients with hydrochlorothiazide because it might
17 make their gout worse, I was told you treat the
18 life-threatening condition first and you worry
19 about the gout later.

20 I think we're in a situation where we don't
21 have a life-threatening disease here, and we're
22 giving therapies that, in many cases, might be

1 life-threatening, and I'm nervous about that. And
2 I'm nervous about it because the rosier picture
3 than perhaps will exist in real life was presented
4 here because of people in the trials and people
5 excluded from the trials.

6 I listened to Lenore talk about those with
7 renal insufficiency, and that's just one
8 comorbidity they've got. They've got lots. And
9 they're also older than many patients in these
10 trials, and I'm nervous for them.

11 I'm also nervous with the depiction of a
12 side effect profile that looks cumulative and not
13 initial to me, which means that the number needed
14 to harm, which was put up as a silly 1 to 64, is
15 more like 1 to 10, if you get a 2 percent rate
16 cumulatively in every several months and you keep
17 treating for repeated gout attacks with this
18 therapy, and the susceptibles get depleted, meaning
19 those who get infections stop getting treated, what
20 the data suggests is that you keep getting an
21 additional 2 percent cumulative incidence here, so
22 that eventually the rate of serious infections with

1 this treatment is very high.

2 DR. O'NEIL: Dr. Suarez-Almazor?

3 DR. SUAREZ-ALMAZOR: Yes. I agree entirely
4 with Dr. Felson and would also like to say that the
5 number needed to harm for overall serious adverse
6 events was 25, and I consider that too high for
7 treatment of a single attack of gout.

8 DR. O'NEIL: Certainly, in looking at the
9 number needed to harm, or at least trying to
10 calculate that for my patients with juvenile
11 arthritis on TNF inhibitors, we're somewhere in the
12 ballpark of 1 in 10- to 1 in 14,000, and certainly
13 that's caused a huge and probably appropriate
14 concern among consumers. And I think 1 to 25 was
15 rather eye-opening for me as well. And we have no
16 data about what's going to happen year 3, 4, and 5
17 down the road when people have had recurrent
18 treatment, treatment courses with the medication.

19 Dr. Mikuls?

20 DR. MIKULS: The number needed to harm, 25,
21 where is that from? Did I miss something? I
22 thought I was 65.

1 DR. SUAREZ-ALMAZOR: No, no. That's for
2 infections, for serious adverse events. I think
3 that was the data presented by the sponsor.

4 DR. O'NEIL: For all SAEs.

5 DR. BUCKLEY: And that is I think a
6 comparison number needed to harm, not an absolute.
7 So that's compared to triamcinolone.

8 DR. MIKULS: That was compared to
9 triamcinolone.

10 DR. BUCKLEY: But if you ask what its own
11 risk is, not the comparison, I imagine those
12 numbers --

13 DR. FELSON: The RA long-term versus placebo
14 was 7 percent. So that's 1 -- what is that? 1 in
15 13, 1 in 14, something like that.

16 DR. MIKULS: So I guess I would just make
17 the comment that is sort of very well-spoken. I
18 just reiterate some of what we heard earlier.
19 Having taken care of many of these patients, I
20 really believe there is nothing surprising here.
21 There really is an unmet need in this area for
22 people who do not tolerate or have problems with

1 NSAIDs or colchicine. This really happens. This
2 happens on a daily basis in our clinics. We need
3 something for these patients.

4 Clearly, infection to me was the one issue
5 that stood out; but, again, not a surprise there in
6 terms of what we know about IL-1 inhibition. I
7 guess I was, frankly, much less concerned or
8 worried with the other areas that are highlighted.

9 I think the uric acid data that was shown in
10 the RA population really I think was very helpful
11 to see. I totally understand the point that was
12 made about the lack of representation of patients
13 with stage 4 CKD, et cetera. They're not in this
14 study. They're excluded on purpose. And that's an
15 issue because those patients are going to get
16 exposed to this medicine. Anybody who thinks
17 they're not, I mean, it happens. And really, the
18 hypertriglyceridemia data was not overwhelming to
19 me.

20 DR. O'NEIL: Dr. Lapteva?

21 DR. LAPTEVA: Yes. I just have one comment
22 to say about the RA data with uric acid. You may

1 have noticed on the slides, when we were presenting
2 the urate serum level with the gout population,
3 because of the intervals, how the uric acid was
4 measured in the gout safety data set, the uric acid
5 was measured at baseline and then at 48 hours and
6 several days. So it was basically a very close
7 measurement after the administration of the drug.

8 In the RA data on the slide that was shown,
9 the uric acid was measured on a biweekly or weekly
10 basis, where you really won't see the fluctuations
11 in uric acid. So that's little bit of a comparison
12 of apples and oranges here.

13 Then the second point is, for the uric acid
14 level changes observed in the gout population, all
15 patients were flaring at baseline, yet the
16 difference was seen in both randomized trials in
17 the randomized setting. No matter how we interpret
18 it right now -- because we don't have much data,
19 whether it's improvement or worsening or
20 fluctuations or whatnot -- in the randomized
21 setting, there is a difference between
22 triamcinolone and canakinumab, and we're not sure

1 what happens long-term.

2 DR. MIKULS: I guess I would just comment
3 back that it's, I think, the sponsor's at least
4 speculation that this is IL-6-driven, et cetera.
5 That's out there in the literature and very
6 interesting. And I wondered, while that was being
7 presented, isn't that a testable hypothesis with
8 data in hand?

9 I think what was presented is not IL-6 data
10 but C-reactive protein data that -- maybe a
11 reasonable surrogate trial for IL-6 is are we
12 seeing this phenomenon in people who are most
13 likely to drop their C-reactive proteins? Because
14 if the sponsors are right, that would be supportive
15 of that hypothesis. And I haven't seen that data
16 so I don't know.

17 DR. LAPTEVA: I agree with you it would be
18 very interesting to know.

19 DR. SHETZLINE: Madam Chair?

20 DR. O'NEIL: Yes, Dr. --

21 DR. PEDUZZI: Peduzzi.

22 DR. O'NEIL: Thank you. Peduzzi.

1 DR. PEDUZZI: As a non-clinician, I just
2 have a question, that if the indication is to give
3 this drug only for the first flare and not
4 repeatedly over time, is there as much of a concern
5 about the safety in terms of serious adverse events
6 in particular infections? I don't know how to
7 interpret that.

8 DR. O'NEIL: Dr. Felson, do you wish to
9 answer that question?

10 DR. FELSON: I can't imagine that this would
11 be on the market and one wouldn't use that
12 repeatedly. These are patients who are flaring
13 repeatedly in their gout attacks. Many of them
14 have very refractory disease. And I think it would
15 naturally be done. You wouldn't just use it once.

16 DR. PEDUZZI: But is that a consideration of
17 the committee, how it would actually be used in
18 actual practice, as opposed to what the indication
19 for its use actually is? I don't know the answer.

20 DR. O'NEIL: I think we are asked to discuss
21 all these aspects of the approvability of this
22 drug, yes.

1 Dr. Buckley?

2 DR. BUCKLEY: I think, looking again at the
3 efficacy and the safety issue, there's -- I agree
4 that this is an agent that potentially offers
5 benefit, maybe to a small group of people but an
6 important group of people.

7 One of the things we've been saying is this
8 is just for pain. But they're in a group of people
9 who cannot get on a urate-lowering drug without
10 flaring, who can't tolerate the flares, and so
11 never get on a urate-lowering agent. So, in a way,
12 their flares are a barrier to adequate long-term
13 treatment.

14 So I think there is a subgroup for whom this
15 class of medicine -- maybe it's a group of patients
16 who can't take corticosteroids or don't benefit. I
17 think there clearly is a niche for this. I think
18 the concern is, given the risks and what we don't
19 know about the risks in patients with more
20 comorbidities, we all feel uncomfortable letting
21 this be used on a widespread basis if there weren't
22 clear restrictions on who it was to be used in and

1 why it was to be used.

2 But although I have concerns about the
3 risks, I don't think that I would say there's no
4 role for this medicine or a medicine of this type.
5 It's just clearly understanding what the risks and
6 benefits are for a particular patient, and I don't
7 know that I have that information completely.

8 DR. O'NEIL: Dr. Gibofsky?

9 DR. GIBOFSKY: I share all of Dr. Buckley's
10 concerns. I share Dr. Felson's concerns. And I
11 think that if this were a drug that were seeking an
12 indication for the treatment of acute gout without
13 modification in the population in whom this is
14 necessary, there's no question that in my mind, the
15 risk would outweigh the benefit.

16 But I think that given the dramatic problems
17 that occur in this population of patients who
18 really do not have alternatives available to them,
19 that in that niche population, I think this drug
20 has demonstrated efficacy. And like Dr. Mikuls,
21 I'm much more willing to look carefully over time
22 at the possibility of adverse events and manage

1 them to the extent that I can.

2 I would want, however, some clarification or
3 restrictive language. I don't think we should be
4 saying urate-lowering therapies. We have only seen
5 this drug essential used with one urate-lowering
6 strategy, and that's xanthine oxidase inhibition,
7 and only with one xanthine oxidase inhibitor,
8 allopurinol. There were three patients with
9 febuxostat, and that really doesn't constitute
10 urate-lowering therapies in my mind, particularly
11 when others are available. And I would definitely
12 want to see that restriction to the extent that
13 this drug would be used in combination with urate-
14 lowering therapies. I wouldn't want it to be
15 generalized.

16 DR. O'NEIL: Dr. Felson? Dr. Kerr?

17 DR. KERR: I would also like some
18 restriction or consideration of the word "on
19 demand" because my concern is a repeated use. And
20 I think it would bode well both for patients and
21 sponsor because, remember, from the data, about 1
22 in 5 patients still required some prednisone dosing

1 as rescue even when they were on canakinumab. And
2 that might not solve or maybe worsen the infection
3 story.

4 I, too, think that the potential here to
5 evaluate in the registry, et cetera, is if we give
6 it to these patients, does it mean I can start them
7 on a urate-lowering therapy sooner? And I think
8 that's the key that needs to be answered as well.

9 DR. O'NEIL: I'm sorry. Could I just ask
10 for your last point again?

11 DR. KERR: If we can control their pain and
12 symptoms quicker, we can get them on urate-lowering
13 therapy maybe sooner because they have recurrent
14 attacks. But maybe if we can delay that time to
15 relapse, we could probably start a ULT sooner.

16 DR. O'NEIL: Other commentary from the
17 panel?

18 [No response.]

19 DR. O'NEIL: All right. To try to
20 summarize, I think the whole panel as a group was
21 concerned about the risk of infection as the main
22 toxicity that needs to be watched and is a concern

1 in this drug.

2 The issue with hyperuricemia may or may not
3 constitute a risk long-term, but the signal is
4 fairly small with respect to clinical risk,
5 although the number appears to be true.

6 The risk about renal function likewise has
7 not shown itself, at least in the short clinical
8 data that we have, short periods of observation, to
9 be a very significant risk, although this does need
10 to be followed as well.

11 The panel expressed concern that the study
12 subjects were less ill than the actual real-life
13 patient population who most need this drug, and
14 that we might be treating a quality of life disease
15 rather than a life-threatening disease with a drug
16 that has the potential of toxicity that may indeed
17 be life-threatening.

18 The other main concern was that the side
19 effect profile that we have seen does not
20 necessarily reflect the fact that this drug will
21 likely be used repeatedly in subjects, and that
22 therefore the side effect profile in real life will

1 be cumulative rather than single events. Yet, at
2 the same time, there's a tenor among the group that
3 there is indeed an unmet need and that the risk of
4 long-term use remains unknown at this point but
5 will definitely need to be observed, at the very
6 least.

7 There was concern about labeling, that the
8 labeling about uric acid-lowering drugs was a bit
9 more expansive, at least using general terms, when
10 all we know about is a single agent, and the
11 restriction was expressed for limiting the "on
12 demand" phrase in the proposed labeling.

13 Did I miss any major points?

14 [No response.]

15 DR. O'NEIL: Okay.

16 Is there anything else that the FDA would
17 wish us to address under this question?

18 [No response.]

19 DR. O'NEIL: All right. The next question,
20 question 3, is a voting question.

21 Considering the totality of data, has
22 canakinumab at a dose of 150 milligrams

1 subcutaneously demonstrated substantial evidence of
2 efficacy for the treatment of gouty arthritis
3 attacks in patients who cannot obtain adequate
4 response with nonsteroidal anti-inflammatory drugs
5 or colchicine? I ask the panel to vote yes, no, or
6 to abstain.

7 [Vote taken.]

8 DR. O'NEIL: If everyone would press one
9 more time because apparently one vote didn't go
10 through.

11 [Vote retaken.]

12 DR. O'NEIL: The results of the vote for
13 this question number 3 were yes, 11; no, 1; and no
14 abstentions. The no was from Ms. Aronson. All the
15 other panelists voted yes. And I would ask the
16 individuals to state their name, state their vote,
17 and make any comments they wish to regarding the
18 reason for their vote.

19 We'll start with Dr. Peduzzi.

20 DR. PEDUZZI: I voted yes. The efficacy
21 data to me clearly show that the effect in
22 canakinumab appears early, and it's sustained for

1 both the co-primary endpoints.

2 DR. FELSON: Dr. Felson. I agreed.

3 DR. NEOGI: Tuhina Neogi. I voted yes. And
4 I agree that the data supports that particular
5 statement. And as discussed before, there are some
6 patient populations in whom we would like to know
7 what the efficacy would be, but the data is not
8 there presently.

9 DR. GIBOFSKY: Gibofsky. I voted yes. I
10 agree.

11 MR. SNARSKY: Snarsky. I voted yes. I have
12 no comment.

13 MS. ARONSON: I voted no because of the word
14 "substantial" and because of the problems with the
15 study inclusion as far as the indication for severe
16 gout patients.

17 DR. O'NEIL: That was Ms. Aronson.

18 DR. SUAREZ-ALMAZOR: Suarez-Almazor. I
19 voted yes. I think there is enough data.

20 DR. BUCKLEY: Lenore Buckley. I voted yes,
21 for the reasons already stated.

22 DR. O'NEIL: Kathleen O'Neil. I voted yes.

1 The efficacy data is sufficient.

2 DR. MIKULS: Mikuls. I voted yes, for the
3 reasons stated.

4 DR. BLUMENTHAL: Blumenthal. I voted yes
5 because I feel efficacy was demonstrated.

6 DR. KERR: Kerr. I voted yes. I think the
7 data are clear.

8 DR. O'NEIL: Thank you.

9 The next question is also a voting question.
10 Considering the totality of data, has canakinumab
11 at a dose of 150 milligrams demonstrated
12 substantial evidence of efficacy for the additional
13 claim that canakinumab has been shown to extend the
14 life -- I'm sorry -- to extend the time to next
15 attack and reduce frequency of subsequent attacks?

16 This is a voting question, and I ask you to
17 press yes, no, or abstain on your pad.

18 [Vote taken.]

19 DR. O'NEIL: The voting results are yes, 8;
20 no, 4; and zero abstentions. Those voting no were
21 Aronson, Blumenthal, Felson, and Suarez-Almazor.

22 Again, we will go around the room. State

1 your name, please, for the record and your vote, as
2 well as reasons for that vote.

3 DR. PEDUZZI: Peduzzi. I voted yes. I
4 think the data are fairly compelling in this
5 particular area.

6 DR. FELSON: Felson. I voted no. I would
7 have preferred to have the two statements broken
8 apart. I think the primary aim of the trial, which
9 I agree was accomplished, was to show that it
10 extended the time to the next attack. That they
11 did very successfully.

12 There was no primary or secondary preplanned
13 aim that addressed reducing frequency of subsequent
14 attacks. That was a post hoc secondary analysis,
15 which evidently was positive. They have not shown
16 that. Had they broken that question into two
17 different questions, I would have been happy to
18 vote yes on the first one.

19 DR. NEOGI: Tuhina Neogi. I voted yes. I
20 think the data shown did support the time to next
21 attack. There is some concern that those on urate-
22 lowering therapy may have less benefit from that,

1 but perhaps might be better addressed by a larger
2 study.

3 DR. GIBOFSKY: Gibofsky. I voted yes. I
4 agree with my colleague to my right.

5 MR. SNARSKY: Snarsky. I agreed. I agree
6 with everyone else.

7 MS. ARONSON: Aronson. I agree with what
8 Dr. Felson has said and was concerned about the
9 lack of data.

10 DR. SUAREZ-ALMAZOR: Suarez-Almazor. I
11 voted no because we are asked to consider the
12 totality of the data, and for these patients with
13 recurrent attacks, the majority should be on urate-
14 lowering drugs. And for those patients, there was
15 no difference at all with triamcinolone in time to
16 attack, so I didn't feel that I could vote yes if I
17 consider the totality of the data.

18 DR. BUCKLEY: Lenore Buckley. I voted yes.
19 The language is somewhat vague -- "extend the time
20 to next attack" -- but I think there's clear data
21 that the action of this drug is prolonged and so
22 offers some protection.

1 I agree with Dr. Felson that I have concerns
2 about the second part of the claim and the end of
3 that sentence.

4 DR. O'NEIL: O'Neil. I voted yes, and I
5 agree fully with Dr. Buckley's statement.

6 DR. MIKULS: Mikuls. I voted yes, with the
7 understanding that I wonder aloud, with the
8 statement separated by itself, whether lower doses
9 can also extend equally the time to the next
10 attack.

11 DR. BLUMENTHAL: Blumenthal. I voted no. I
12 had some of the same concerns that Dr. Felson had.
13 And I also don't feel that triamcinolone
14 40 milligrams is a very good comparator for a study
15 with this purpose in mind because that medication
16 would not be expected to have that result.

17 DR. KERR: Kerr. I voted yes because I
18 thought the data supported that, for the reasons
19 stated. But, again, long-term data would provide
20 more insight into that whole subject.

21 DR. O'NEIL: Our next question --

22 DR. OKADA-YIM: Madam Chair?

1 DR. O'NEIL: Yes?

2 DR. OKADA-YIM: Could I just ask a
3 clarification on, for those voting no, what
4 additional data they think should be obtained?

5 DR. O'NEIL: That question stands.

6 Dr. Kerr, would you like to comment? I'm
7 sorry. Dr. Blumenthal?

8 DR. BLUMENTHAL: I think I would prefer to
9 have that question addressed in a study where
10 that's the primary endpoint of the study, with a
11 proper comparator.

12 DR. O'NEIL: Dr. Suarez-Almazor?

13 DR. SUAREZ-ALMAZOR: I agree with that. And
14 I would also like to have more data as to why some
15 of these patients were not on urate-lowering drugs;
16 and also, with the new agent that we have,
17 febuxostat, what happens in that case.

18 DR. O'NEIL: Ms. Aronson?

19 MS. ARONSON: Perhaps a review of lower
20 doses for subsequent clinic attacks, and then just
21 evaluating the half-life regarding efficacy and
22 sort of figuring that component out.

1 DR. O'NEIL: Dr. Felson?

2 DR. FELSON: I don't have any additional
3 suggestions. I think the comments were fine, were
4 good.

5 DR. O'NEIL: Thank you.

6 For the next question, I will read the
7 question, and then if there are any issues
8 regarding discussion, we'll have a moment to
9 discuss that question a bit further because I think
10 it's a bit more complicated.

11 Question 5. Is the safety profile of
12 canakinumab sufficient for approval of canakinumab
13 for treatment of gouty arthritis attacks in
14 patients who cannot obtain adequate response with
15 NSAIDs or colchicine? This is a voting question,
16 but first we will discuss.

17 Dr. Neogi?

18 DR. NEOGI: I think I echo other people's
19 comments that the patient population may need to be
20 better defined. In my mind, I'm thinking about
21 this drug in the setting of those patients where
22 every two months I have to have them on a course of

1 prednisone. And I think the long-term adverse
2 effects of repeated courses of oral prednisone may
3 have even more adverse effects and infection risk
4 and fraction risk and cardiovascular risk, et
5 cetera, et cetera.

6 So, for me, although we cannot compare the
7 safety profile with the data at hand, that would be
8 the patient population that I'm thinking of.

9 DR. O'NEIL: Dr. Felson?

10 DR. FELSON: I think the problem is that the
11 phrase is nonsteroidals or colchicine. I think
12 we're all probably thinking it might be nice to
13 find a subset of patients that we could target for
14 this because I think we all recognize there may be
15 some subset of patients out there. But the way
16 this is written, you can get a little bit of
17 colchicine, which many long-term gout patients
18 don't respond to, and you can be 70 years old with
19 a lot of comorbidities and a lot of renal
20 dysfunction, and you can get this treatment. And
21 I'd be nervous about that.

22 I don't know exactly how to change the

1 wording or rephrase it. But the wording there is
2 just not -- it's too liberal in terms of allowing
3 too many people, and not restrictive enough.

4 DR. O'NEIL: Dr. Mikuls?

5 DR. MIKULS: Can I ask a clarifying
6 question? Question 5, as it's on the screen or at
7 least in front of me, says "recurrent acute gout
8 attacks." That's not what it says on the sheet.

9 So which is correct? The question on the
10 screen?

11 DR. OKADA-YIM: The question on the screen,
12 please.

13 DR. O'NEIL: Sorry. It's in my poor vision
14 zone. The question on the screen is, is the safety
15 profile of canakinumab at a dose of 150 milligrams
16 sub-Q sufficient for approval for use as acute
17 recurrent treatment of gout flares in the
18 population of gout patients who cannot obtain
19 adequate response with nonsteroidals or colchicine?

20 Dr. Blumenthal?

21 DR. BLUMENTHAL: I'm interested in a
22 clarification from the FDA about how we should

1 vote. It seems like there are some members of the
2 committee who have a very specific idea of which
3 patients in their practice would be excellent
4 candidates for this product, but the labeling is
5 going to be for a group that's defined fairly
6 broadly.

7 It can be used by practitioners who are not
8 as thoughtful, perhaps, as many of the
9 rheumatologists in this room about just what
10 population is supposed to receive this drug, and
11 they may not get uric acid-lowering therapy.

12 So if a member of the committee has concerns
13 that the mandate may be too broad, but we do see a
14 niche role for the drug, how do we vote on a
15 question that is worded this way?

16 DR. OKADA-YIM: I'm sorry. I was
17 interrupted there for a second.

18 Would you repeat the last part of your
19 question?

20 DR. BLUMENTHAL: I can see some members of
21 the committee potentially using this drug in
22 certain of their patients, but at the same time

1 being uncomfortable with opening its use to a
2 variety of practitioners in any patient who is
3 defined as unsuitable for either NSAIDs or
4 colchicine. That may be too broad a mandate for
5 members of the committee.

6 So when a question is phrased exactly this
7 way, if you're uncomfortable with how broad the
8 mandate is, do you vote no; or do you vote yes
9 because you see a role for the drug, and then in
10 the discussion to follow we limit the future
11 patient population that would receive it?

12 DR. OKADA-YIM: So I would just remind you
13 all that the indication is a reflection of the
14 patient population in the trials. I think we all
15 agree that this treatment could have a potential
16 role to play in the treatment of patients with
17 gout. The question is, do we have data to support
18 the role that we think is appropriate?

19 So the indication reflects the patient
20 population. I guess I don't know quite how to tell
21 you how to vote. But it is an accurate reflection
22 of the data we have.

1 DR. O'NEIL: Dr. Chowdhury?

2 DR. CHOWDHURY: I'm Dr. Chowdhury. Just to
3 reflect back a bit more on that, this indication is
4 phrased by the company and conceptually driven by
5 the patients enrolled in the trial, as we just
6 heard. And what you're reflecting in your voting
7 here is not necessarily how one person -- you, for
8 example, here -- would use the drug. You're
9 actually making a recommendation for the use of the
10 drug for the U.S. physicians larger.

11 So that public health mindset needs to play
12 in that this is for, as it is proposed here, all
13 physicians to use. So that's the context by which
14 you would vote. And depending on which way you
15 vote is your choice. You can actually put some
16 explanatory notes or some comments for us to hear,
17 and we can take it from there and see if we can
18 craft in language that would take into
19 consideration how you voted and what your comments
20 were, and can you make it in any way restrictive
21 whenever you feel it appropriate. But the voting
22 should be based on what it is.

1 Again, this is the way we are dealing with
2 this application again. In fact, the application,
3 this is not necessarily very simple and
4 straightforward. Thank you.

5 DR. O'NEIL: Dr. Blumenthal, did you have
6 another question or comment?

7 DR. BLUMENTHAL: I think what we're hearing
8 is that someone who feels that the indication is
9 stated too broadly, I think, as I understand it,
10 they are supposed to show their discomfort with
11 that by voting no, and not vote yes with a narrow
12 group of patients in mind and then afterwards try
13 to impose the restrictions that they would like on
14 this indication.

15 Am I right?

16 DR. CHOWDHURY: You are right. I mean, that
17 actually helps us a lot, to be this clear voting
18 based on the question, and then give explanations,
19 which is really, really very helpful to us to
20 understand if we can get to a crafted question
21 population.

22 We're not here to recreate the indication

1 and vote on that. We don't have the luxury of the
2 time to do that. So vote as you see it, and then
3 give us, naturally, comments.

4 DR. O'NEIL: Dr. Fletcher?

5 DR. FLETCHER: I would just point out -- and
6 I think Dr. Blumenthal again points very clearly at
7 the quandary here. But I'd point back to the
8 actual group of patients and the demographics.
9 These individuals had six or seven flares per year,
10 so I would think incorporating in the label and the
11 discussion of how to inform individuals, the label
12 would need to be strong, and I think the company
13 would certainly support having the characterization
14 of the patient groups such as this patient.

15 I mean, you get what you study, generally,
16 and the group of patients here are the ones that
17 we're really talking about. And I think the six or
18 seven flares per year kind of constitutes a strong
19 aspect of that and should be in the consideration
20 of how the label is informed, either in the
21 clinical section or the label indication.

22 DR. O'NEIL: Ms. Aronson?

1 MS. ARONSON: I really appreciate and thank
2 Dr. Blumenthal for helping to crystallize some of
3 the issue here. As a consumer representative, I
4 started off -- my worry is sort of the
5 advertisement of the indication and folks rushing
6 in to physicians to demand. It sounds really good.

7 So I guess knowing that it's supposed to be
8 for a really restricted population sets a quandary
9 for me on how broad the indication seems to be.

10 DR. O'NEIL: Yes, Dr. Peduzzi?

11 DR. PEDUZZI: I just have a question. What
12 are we actually voting on? Because that's
13 different from what is on the sheet.

14 DR. O'NEIL: We are to vote on what is on
15 the screen because that apparently is the latest
16 question.

17 DR. PEDUZZI: What's on the screen.

18 DR. O'NEIL: Dr. Yim?

19 DR. OKADA-YIM: Let me just clarify. We did
20 try to take it away a little bit from the exact
21 wording of the indication to the more principle of
22 the matter, which is acute recurrent treatment for

1 the population that the sponsor is proposing.

2 So I guess, really, the vote regarding
3 safety is intended to be captured by the question
4 on the screen rather than the exact wording of the
5 indication.

6 DR. O'NEIL: If there is no further
7 discussion, then I will call to vote. And I ask
8 the panelists to vote yes, no, or abstain.

9 [Vote taken.]

10 DR. O'NEIL: The panel is unanimous in
11 voting no, with no abstentions and no yes votes.

12 I would again ask the panelists, the voting
13 members, to state their name and state into the
14 record their vote, as well as the reasons or
15 clarifications of their vote.

16 Let's start on this side with Dr. Kerr,
17 please.

18 DR. KERR: I voted no. I thought that there
19 was insufficient data, too few numbers, especially
20 with recurrent therapy, to answer the questions of
21 any increased safety concerns on the baseline
22 safety signals that existed.

1 DR. BLUMENTHAL: This is Blumenthal. I
2 voted no because I have the same concerns about
3 safety. And I feel that the sponsor has identified
4 the potential population for this medication too
5 broadly.

6 DR. MIKULS: So my enthusiasm about
7 potential utility of this drug in very difficult
8 patients is clearly tempered by what I saw as a
9 lack of reassuring data that I'd like to see for
10 recurrent use. We were presented data essentially
11 on 43 patients, the really solid, recurrent dosing,
12 and I just don't -- just were not enough for me.

13 DR. O'NEIL: I'm O'Neil, and I also voted
14 no. My feeling is as Dr. Mikuls stated and
15 Dr. Blumenthal stated, but I also have concerns
16 about not just the breadth of the definition of the
17 population for whom this was indicated, or proposed
18 as indicated, but also with the small number of
19 subjects observed with repeated dosing, and for
20 only six months of follow-up data, really, at this
21 point.

22 I think, looking back at what we were

1 instructed by Dr. Okada-Yim about the FDA
2 regulations, we have not met the burden of proof of
3 showing that this is a safe drug for that
4 population.

5 DR. BUCKLEY: I'm Lenore Buckley. I voted
6 no. I guess what I would like to see is a
7 broadening of restrictions. So I think this should
8 be limited to a patient population who cannot use
9 either because of intolerance or risk, NSAIDs,
10 colchicine, and steroids.

11 I think we need a lot more data on patients
12 with comorbidities that predispose to infection,
13 particularly chronic kidney disease, diabetes. And
14 there's a huge population of patients, transplant
15 patients, who would be candidates for this drug who
16 are already immunosuppressed, and we don't know the
17 effect of giving them additional immunosuppression.

18 It's of course not just that. There's also
19 patients with psoriasis on methotrexate who might
20 get this drug, so transplant and other patients who
21 are already taking immunosuppression.

22 DR. SUAREZ-ALMAZOR: Suarez-Almazor. I see

1 two issues for the broad population as it is
2 described here. I think that the risk/benefit
3 ratio is not appropriate even for a single
4 treatment.

5 I also agree, like the rest of the group,
6 that there's probably room for use of this drug;
7 there's a niche and there's a specific population
8 that could benefit from that. But I would like to
9 see at least two- or three-year data with respect
10 to long-term safety with recurrent use.

11 MS. ARONSON: I voted no, and am in
12 agreement with the issues raised, particularly by
13 Dr. Buckley.

14 MR. SNARSKY: Snarsky. I'm afraid of
15 the -- I voted no. I'm afraid of the side effects
16 long-term.

17 DR. GIBOFSKY: Gibofsky. I voted no. The
18 dichotomy between the population in a clinical
19 trial and the population in clinical practice is
20 well-known to us, and we often end up using drugs
21 in clinical practice on patients that would have
22 been excluded from clinical trials.

1 That doesn't concern me as much as the
2 breadth of the definition, which suggests that
3 since more gout is treated by a non-specialist than
4 by a specialist, the number of people who will be
5 using this drug is potentially broader than the
6 number of people who are using biologics in our
7 specialty.

8 Consequently, I just worry that the nuances
9 that we're discussing today about a biologic
10 therapy in this population will not be entirely
11 known to them, and thus the breadth of the
12 labeling concerns me. I think we need much more
13 specificity on it.

14 DR. NEOGI: Tuhina Neogi. I voted no.
15 Although I have great enthusiasm for opening up
16 options for management of acute and chronic gout in
17 difficult-to-manage patients, I agree with the
18 prior comments regarding the small numbers that had
19 recurrent therapy and not enough long-term data,
20 the need for a study in specific patient
21 populations, wanting to have the label be more
22 specific for the patient population, although as

1 rheumatologists I think we're comfortable with
2 using biologics. And I would argue that many of
3 these patients that we're talking about for this
4 indication have much more functional limitations
5 than the RA patients that we're treating with
6 biologics. But I think we need more data to
7 support that.

8 DR. FELSON: This is Dr. Felson. I'll
9 second the need for additional safety data. I
10 think 43 patients with recurrent treatment is just
11 too small a number for us to be confident that this
12 is going to be safe for people over time.

13 I also would raise the question, or the
14 issue not yet raised, as to whether the patient
15 like the one Dr. Wortmann presented earlier today
16 are historical people now because of the
17 availability of more effective urate-lowering
18 therapies that are going to be more widely used.
19 And I wonder if a therapy like this, five years
20 down the road, is going to really be all that
21 critical, but I'm not sure.

22 DR. PEDUZZI: Peduzzi. I voted no. I don't

1 think there's enough safety data for retreatment.
2 However, I feel a little bit otherwise if it was
3 only given as a single treatment.

4 DR. O'NEIL: Dr. Neogi?

5 DR. NEOGI: May I just ask a question?

6 I am not familiar with the opportunities to
7 also have restrictions on who can prescribe. So
8 although gout is largely managed by primary care,
9 if this kind of agent were to be considered for
10 approval, could it be through certain specialties
11 or licensed physicians that would have more
12 expertise in this kind of difficult patient
13 population?

14 DR. CHOWDHURY: That really is not for
15 discussion or for consideration here. That really
16 gets into a situation of REMS and the distributions
17 and all. And the labeling and the proposal like we
18 have on the table here does not really bring that
19 aim into the play. So we are looking at it for a
20 wider use at this time.

21 DR. O'NEIL: So to quickly summarize, there
22 appeared to be a universal no, that this has not

1 yet proved to be sufficiently safe for labeling as
2 indicated on the screen. However, there also
3 appeared to be fairly universal enthusiasm for this
4 drug being available for a limited patient subset,
5 but that further data is really needed to feel
6 comfortable.

7 DR. CHOWDHURY: One comment regarding what
8 further data is necessary. We heard quite a bit of
9 discussion about long-term data and data in
10 patients with other comorbid conditions. I would
11 appreciate if you can ask around if there's
12 anything else we need to hear from the committee on
13 that.

14 DR. O'NEIL: Good question.

15 Dr. Buckley, we'll start with you and go
16 that way.

17 DR. BUCKLEY: I think I've already stated
18 before the things that I would consider. I would
19 probably add, and I'm sure others have more to add,
20 cardiovascular, a little bit more long-term
21 follow-up of cardiovascular risks and the renal
22 function risks.

1 DR. SUAREZ-ALMAZOR: Same, and also
2 infections.

3 MS. ARONSON: Just more information
4 about --

5 DR. O'NEIL: Please state your name.

6 MS. ARONSON: Oh, sorry. Diane
7 Aronson -- about the increase in uric acid impact.

8 MR. SNARSKY: Snarsky. I'm just not happy.

9 DR. O'NEIL: Gibofsky. Renal function and
10 cardiovascular risks.

11 DR. NEOGI: Neogi. I agree with the prior
12 comments.

13 DR. FELSON: I don't have anything to add.

14 DR. PEDUZZI: I don't have anything further
15 to add.

16 DR. O'NEIL: Dr. Kerr?

17 DR. KERR: I think I agree with the rest.
18 But I would like to see older patients in this, and
19 probably even more patients included who actually
20 have tophi because I think that's more
21 representative.

22 DR. BLUMENTHAL: I think I'd want to see

1 data on the populations that are likely to be
2 considered for this drug, diabetic patients,
3 patients with more significant renal insufficiency
4 than what was present in this study, postoperative
5 patients, for example.

6 DR. MIKULS: Mikuls. I don't have anything
7 to add.

8 DR. O'NEIL: O'Neil. The one thing I have
9 to add is that I think we need longer safety data,
10 particularly on the repeated dose patients;
11 sufficiently specific. Thank you.

12 Question number 6. Do the efficacy and
13 safety data provide substantial evidence to support
14 approval of canakinumab at a dose of 150 milligrams
15 subcutaneously for "treatment of gouty arthritis
16 attacks in patients who cannot obtain adequate
17 response with NSAIDs or colchicine"?

18 We have time for some discussion on this,
19 and I think it is probably warranted.

20 Dr. Felson? Oh, you were reaching for
21 water, not for the microphone.

22 [Laughter.]

1 DR. O'NEIL: Well, I'll speak, then. I
2 think discussion is probably warranted because I
3 think, here again, we're going to have concerns
4 about balancing a strong efficacy signal with a
5 weak safety signal. And that makes it very hard to
6 support approval for something as broadly stated as
7 "treatment of gouty arthritis attacks in patients
8 who cannot obtain adequate response with NSAIDs or
9 colchicine."

10 I think the other issue is that there's
11 nothing recommending it as part of a program with
12 uric acid-lowering agents. We don't have that much
13 data about uric acid-lowering agents. And I think
14 I have a question for the FDA based on this sort of
15 global discomfort at trying to balance something
16 that I can't even get in my hand firmly.

17 My question to the FDA is, what you're
18 asking us to vote on is what we see on the screen,
19 nothing more, nothing less.

20 Is that true?

21 DR. OKADA-YIM: Yes. That is what we're
22 asking you to vote on. However, I would like to

1 clarify that if you vote no on that particular
2 question, but you believe that you could cobble
3 together something more restrictive from the
4 clinical trial data that we have available, then
5 we'd like to hear that in the explanation as
6 follow-up to your vote.

7 DR. O'NEIL: In other words, if we feel that
8 we could vote yes for a different statement, then
9 we'd tell you that?

10 DR. OKADA-YIM: Yes. But I would ask that
11 it be supported by available clinical trial data.
12 We can't just go for a different population that we
13 don't have data for.

14 DR. CHOWDHURY: Again, just a comment here.
15 Just to add on further to that, you can vote any
16 way you want to. But if you see a different
17 patient population that you think the drug may
18 actually be reasonable for approval, you can make
19 that as a comment, which is very important to us.

20 Again, keep in mind, as you're waiting for
21 approval, it is just not efficacy. It's efficacy
22 and safety. So both has to, in your own mind,

1 pass. Thank you.

2 DR. O'NEIL: Dr. Gibofsky?

3 DR. GIBOFSKY: I just want clarification
4 from Dr. Chowdhury as to whether we're also able to
5 comment on issues as were brought up by my
6 colleague to my right about restricted
7 distribution, restricted utilization, and who will
8 be defining the population who will be getting the
9 drug. Because I think the enthusiasm for its use,
10 coupled with concern about the safety, do indicate
11 that this drug is an agent that could be used
12 appropriately in a specific population if that
13 population was specifically defined, and the
14 population of people who were defining that
15 population were specifically defined.

16 [Laughter.]

17 DR. CHOWDHURY: The answer to that question
18 is yes. I mean, after you vote, you certainly
19 would make comments. And in that comment, you can
20 try to define for us what you think would be the
21 patient population or conditions for use. And we
22 will take that into advisement and think through it

1 and see if something can be achieved based on your
2 or those comments.

3 DR. O'NEIL: So I remain -- and I'm probably
4 not the only one on the panel who remains a little
5 bit confused; so that if we, like Dr.
6 Gibofsky -- if I, like Dr. Gibofsky -- feel that
7 there is a niche for this drug, that I would like
8 to see this drug approved, but I would like to see
9 it for a tighter indication based on the clinical
10 data that we are presented with, or the clinical
11 trial data, and my global discomfort with some of
12 what I see in clinical practice that gets referred
13 to me eventually.

14 I guess my concern is I don't know whether
15 to vote yes or no in that setting and then clarify.

16 DR. CHOWDHURY: Again, I think the easiest
17 for us would be to look at the question as it is,
18 and we already discussed efficacy and safety and
19 voted on that. So put the two together into the
20 voting of this question. So it really is a
21 synthesis of the two questions that you discussed
22 before and voted. And fully understanding from

1 acknowledging what you are saying is, can you find
2 a niche, a different indication, so some sort of
3 condition that would make one comfortable? And
4 that is actually for the discussion portion and for
5 you to discuss here and let us know. So we will
6 take that into consideration as we internally
7 discuss and think about it further. So that
8 portion would be for your comments.

9 Am I clear enough?

10 DR. O'NEIL: I think so, but I still don't
11 know whether to vote yes or no.

12 Dr. Fletcher?

13 DR. FLETCHER: I wonder, just as an example,
14 if people are thinking about defining a population
15 that, obviously, the patients who can't use the
16 colchicine or NSAIDs but who have the number 3 to 5
17 or whatever was in the criteria or the protocol,
18 have that more defined in the patient group.

19 Would the committee in general -- is that
20 the kind of thing that could be asked for or
21 recommended after the vote?

22 DR. OKADA-YIM: Yes. I think that's what I

1 was getting at. Once you vote on this particular
2 indication, if you think that there is an
3 indication that could be obtained from the clinical
4 trial data, then mention it, and that
5 certainly -- or if there are measures that you
6 think would justify approving it with those
7 measures, that would be the time to mention those.

8 DR. CHOWDHURY: Let me clarify one point
9 further. What we're looking for, and again
10 Dr. Okada mentioned, is if you think a different
11 indication, so some of the conditions would make it
12 favorable, make that as a comment; but again,
13 keeping in mind what the clinical trial data shows,
14 and not -- this isn't to create another group,
15 which may be a hypothetical group for which one can
16 craft an indication, but that group has not been
17 studied. We don't necessarily want one to go
18 there. It's based on what is available based on
19 existing clinical trial data that we discussed
20 here.

21 DR. O'NEIL: Are we ready to proceed? I ask
22 you all now to vote yes, no, or abstain.

1 [Vote taken.]

2 DR. O'NEIL: The results are shown on the
3 screen, 1 yes, 11 noes, zero abstentions. The
4 1 yes was from Dr. Gibofsky. All others voted no.

5 Let us proceed around the table again.

6 Dr. Buckley, could you start, please?

7 DR. BUCKLEY: I voted no because I didn't
8 think we had enough data about high-risk patients
9 in which this drug is most likely to be used. I'm
10 on the fence about whether we can craft a group
11 with the current data where I would feel
12 comfortable prescribing it.

13 If I were to begin to craft that statement,
14 it would be patients who have 6 or more attacks of
15 gout a year; who have good renal function and do
16 not have other significant comorbidities; who
17 have -- and I would use the "and" rather than the
18 "or" word -- in whom you are not able to use
19 NSAIDs, colchicine, or steroids because of either
20 side effects or contraindications.

21 But to be honest, I'm still quite
22 uncomfortable about how broadly this may be used in

1 practice unless restrictions are put on about who
2 might prescribe it, as has already been discussed.

3 DR. SUAREZ-ALMAZOR: Yes. I voted no
4 because I'm uncomfortable with the risk/benefit
5 ratio, as stated before. And again, these would be
6 used for a non-life-threatening condition, and even
7 if we were to define recurrent attacks as six per
8 year, we only have data on 43 patients that
9 received three, or I think a couple of them
10 received more than three, treatments. So there's
11 not enough long-term safety data to give me the
12 comfort of voting yes.

13 DR. O'NEIL: So that was Dr. Suarez-Almazor,
14 for the record. And I'm going to ask you to
15 clarify that you do not feel that you could define
16 a population for whom you would vote yes.

17 DR. SUAREZ-ALMAZOR: With the current safety
18 data, I wouldn't be able to. I don't know that
19 that necessarily means that I would need another
20 clinical trial. I would have liked to see more
21 long-term follow-up data in the current
22 participants, as opposed to just six months of

1 data. I don't know if that data is or will be
2 available.

3 MS. ARONSON: Diane Aronson. I voted no.
4 As the indication is written, it is broad, and I
5 have concerns about that; and also concerns about
6 not enough information regarding risks with
7 patients with severe comorbidities.

8 MR. SNARSKY: Snarsky. I voted no. I just
9 don't feel comfortable. I don't think it's quite
10 ready to go out there.

11 DR. GIBOFSKY: Gibofsky. I voted yes. I
12 think that we can craft a population along the
13 lines of what Dr. Buckley approached, with some
14 modifications, and I think we can combine it with a
15 vigorous REMS program, along the lines with
16 elements to assure safe use that the agency's
17 familiar with.

18 I would not want to see the population of
19 patients who would benefit from this drug not get
20 it because of the possibility of overuse by other
21 individuals, and I think we can control that. I
22 really do think we can. Were this a criminal case,

1 this patient, this individual, would be acquitted
2 right now. So I think we should be moving in that
3 direction.

4 DR. NEOGI: Neogi. I voted no. As I said
5 before, I have great enthusiasm for increasing the
6 options for managing difficult gout patients. I
7 think the efficacy data is promising. I was
8 concerned about the recurrent use with just a
9 limited number of participants in these studies and
10 not enough long-term data.

11 In thinking about the existing trial data,
12 if we think about people who have four to six
13 attacks per year, who are unable to take NSAIDs or
14 colchicine or have inadequate response to NSAIDs or
15 colchicine, those are the people that are going to
16 be exposed to repeated steroids.

17 So in addition to wanting additional safety
18 and efficacy data in the populations already
19 discussed, I think from this trial data, for
20 participants who would be exposed to repeated
21 courses of steroids otherwise, therefore
22 meaning -- the indication would be unable to obtain

1 adequate response to NSAIDs and colchicine.

2 DR. FELSON: I voted no, and I don't have
3 anything that novel to add. But I wanted to sort
4 of suggest that additional data -- so there are
5 obviously two issues here. One is restriction, and
6 Lenore proposed a very nice set of rules for that,
7 I thought, that included colchicine and
8 nonsteroidals and steroids. I thought that was
9 important. And then the other issue was safety
10 information.

11 I think I would couple those two together in
12 suggesting additional data, meaning that since the
13 difficult patients here are the ones that are
14 likely to be treated and that may need this, or may
15 be ones who weren't so eligible for that trial,
16 that additional data, if we could encourage it,
17 might be collected in those who would meet Lenore's
18 criteria and who would likely be the ones we'd want
19 to treat. And then we'd want to know what kind of
20 safety profile we were getting from those patients.

21 I realize that may be beyond an efficacy
22 trial, but I think we're trying to tell you that

1 efficacy, at least in the patients in the trial,
2 has been shown, and that the issues that are
3 paramount here are safety concerns, especially in a
4 group that wasn't necessarily so well represented
5 in the trial.

6 DR. PEDUZZI: Peduzzi. I voted no for
7 reasons that have already been discussed.

8 DR. KERR: Kerr. I voted no as well because
9 I still had discomfort with the safety. I would
10 think of using this drug in a select group of
11 patients. But if I'm to vote on the data presented
12 here today, those patients are not represented
13 there. And therefore, that was my hesitation.

14 I think the inclusion of "and" is very
15 important because very few patients in the study
16 actually failed NSAIDs and colchicine. The
17 majority were either/or. So I think, again, it was
18 a select group, and we may not be seeing the true
19 safety signal in the patients who actually need the
20 drug.

21 DR. BLUMENTHAL: Blumenthal. I voted no
22 because I felt that the statement on the screen was

1 something that I could not support with a yes vote.
2 I do see a potential role for this drug, but not
3 for the indication as it was stated by the sponsor
4 in this forum.

5 I think the true target population for this
6 drug is, as Dr. Buckley said, patients who are not
7 candidates for nonsteroidals, colchicine, or
8 corticosteroids; none of those, and then you move
9 on to the possibility of using this drug.

10 But I cannot use the currently available
11 data to judge whether this drug is ready to be used
12 in that population because that's not specifically
13 what they studied. And I have the same concerns
14 about long-term efficacy that have been stated, so
15 that additional study of the drug would have to
16 include longer-term follow-up data for me to be
17 able to support it.

18 DR. MIKULS: Mikuls. I voted no, yet I
19 almost agreed completely with Dr. Gibofsky, who
20 voted yes. I think where we parted ways was I
21 believe fairly strongly that the recurrent use
22 issue is there, and I don't think we can get that

1 back once that's out of the barn, so to speak, so
2 we need to see much more rigorous data in that
3 regard.

4 I don't think the trial data would answer
5 this necessarily, but where I would see using this
6 in clinic tomorrow if I had it was a patient -- I
7 have many patients, and I'm sure many of the
8 experts in the room, who we just cannot get started
9 on urate-lowering therapy. They have advanced
10 gout, as was eloquently shown earlier. This cannot
11 get them bridged over effectively to urate-lowering
12 therapy without recurrent flares. And this is an
13 agent that could really help us do that. So I'd be
14 very excited about having that ability.

15 DR. O'NEIL: This is Kathleen O'Neil, and I
16 voted no because I, like most of my colleagues,
17 could not vote for the statement as it stood on the
18 screen.

19 I also share the enthusiasm that many of my
20 colleagues have for the potential of this highly
21 efficacious drug. And I'm also perhaps even more
22 impressed than some with the long-term -- and I use

1 "long-term" in quotations because we're talking six
2 months -- efficacy with regard to the question
3 about decreasing the -- or increasing the interval
4 to the next flare, and somewhat softer but apparent
5 increase in the -- or decrease in the number of
6 flares over that period of time.

7 I think we -- I would like to think, but
8 it's going to take someone with a better
9 statistical mind than me, to look at the existing
10 subjects who remain in the trial and see if perhaps
11 we can get sufficient information in another, say,
12 six months or so that will give us more than 43
13 subjects who have been treated more than twice.

14 I think the safety signal is a concern, but
15 when you look -- I have a poor man's common-sense
16 approach to most of the statistics that other folks
17 find fantastic formulas to figure out. But
18 generally speaking, if you can take two or three
19 people from column A and move them to column B and
20 get equal results when there appears to be a
21 difference initially, then you don't have any
22 statistical significance, at least no biologic

1 significance, to me.

2 That was generally the case with the small
3 number of AEs and SAEs, even though some of them
4 were a little bit concerning. And the ratios
5 looked big, but the actual data looked weak just
6 because of the low number of problems, which I
7 think is somewhat reassuring, but not completely.

8 So I would like to see what would happen in
9 the next six months of follow-up, which I believe
10 was hinted that you are still collecting these data
11 on the patients in the two pivotal trials. That
12 may be sufficient to answer the questions that were
13 raised or many of the questions that were raised by
14 my colleagues.

15 I don't think we will know until it is
16 available, however, and whether the other
17 populations that weren't entered into the trial
18 will have unique safety signals or fantastic
19 efficacy signals, even.

20 So in balancing -- and what we were told to
21 do was to balance safety and efficacy -- efficacy
22 is way down here -- or way up here; I don't know.

1 It depends on how it looks. But safety,
2 unfortunately, is a weakness in the data we were
3 presented, and I think we need something better to
4 support that.

5 We have one more question. Do the efficacy
6 and safety data provide substantial evidence to
7 support approval of canakinumab at a dose of
8 150 milligrams subcutaneously for the additional
9 claim that canakinumab has shown to extend the time
10 to next attack and reduce frequency of subsequent
11 attacks?

12 Is there discussion/debate over this
13 question?

14 [No response.]

15 DR. O'NEIL: Shall we proceed to vote?
16 Again, your options are yes, no, and abstain.

17 [Vote taken.]

18 DR. O'NEIL: The results are zero yes;
19 12 no; zero abstentions. And I think we can
20 probably fairly quickly run around the room and
21 give our comments, but I think the comments are
22 important to the FDA.

1 Dr. Kerr?

2 DR. KERR: I voted no, and the previous
3 discussions I think adequately answer this
4 question.

5 DR. BLUMENTHAL: I have the same safety
6 concerns as we just discussed with the last
7 question. And because of that, it's hard to vote
8 yes for something that was not even a primary
9 endpoint of the original study.

10 DR. MIKULS: Mikuls. I voted no. Not much
11 to add to what's been said. Clear efficacy to me,
12 actually, maybe in contrast. Same safety concerns
13 we've discussed.

14 DR. O'NEIL: O'Neil. Same issues. Yes for
15 efficacy, no for safety; therefore, no for the
16 balance.

17 DR. BUCKLEY: Buckley. Not enough long-term
18 data on efficacy and same safety concerns.

19 DR. SUAREZ-ALMAZOR: Suarez-Almazor. I
20 voted no, for the reasons stated.

21 MS. ARONSON: Diane Aronson. I voted no for
22 the reasons stated.

1 sponsors for their clear presentation of what looks
2 to be a promising drug but is -- and hopefully soon
3 we'll have the data to support that, and the FDA
4 for also their clear presentations.

5 DR. OKADA-YIM: And we'd very much like to
6 thank the committee for their careful consideration
7 this afternoon. Thank you.

8 (Whereupon, at 3:45 p.m., the meeting was
9 adjourned.)
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