

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION CENTER
FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE
BLA STN 103950 KINERET (ANAKINRA), AMGEN, INC.

OPEN SESSION

Thursday, August 16, 2001

8:15 a.m.

Holiday Inn Gaithersburg
Goshen Room
Two Montgomery Village Avenue Gaithersburg, Maryland

PARTICIPANTS

E. Nigel Harris, M.D., Acting Chairperson
Kathleen Reedy, Executive Secretary

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William D. Schwieterman, M.D. Jay P. Siegel, M.D.
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1 P R O C E E D I N G S

2 Call to Order and Introductions

3 DR. HARRIS: I would like to welcome you
4 and begin our morning session. We will start by
5 introducing members of the committee, and I will
6 start from my left.

7 DR. ELASHOFF: Janet Elashoff,
8 biostatistician, Cedars-Sinai and UCLA.

9 DR. ABRAMSON: Steve Abramson,
10 rheumatologist, NYU and the Hospital for Joint
11 Diseases.

12 DR. KATONA: Ildy Katona, pediatric
13 rheumatologist, the Uniformed Services University.

14 DR. FELSON: David Felson, rheumatologist,
15 Boston University School of Medicine.

16 MS. MALONE: Leona Malone, patient
17 representative.

18 DR. WILLIAMS: Jim Williams,
19 rheumatologist, University of Utah.

20 DR. ANDERSON: Jennifer Anderson,
21 statistician, Boston University.

22 DR. HARRIS: I am Nigel Harris,
23 rheumatologist, Dean of Morehouse School of
24 Medicine.

25 MS. REEDY: Kathleen Reedy, Executive

1 Secretary of the Arthritis Advisory Committee for
2 Center for Drugs Evaluation and Research, Food and
3 Drug Administration.

4 DR. BRANDT: Ken Brandt, rheumatologist,
5 Indiana University School of Medicine.

6 DR. CALLAHAN: Leigh Callahan, outcomes
7 researcher and epidemiologist, University of North
8 Carolina, Chapel Hill.

9 DR. WOFSY: David Wofsy, rheumatologist,
10 University of California/San Francisco.

11 DR. DONNELLY: Ray Donnelly, Division of
12 Therapeutic Proteins, Center for Biologics.

13 DR. SIEGEL: Jeff Siegel, clinical
14 reviewer, Division of Clinical Trials, CBER.

15 DR. SCHWIETERMAN: Bill Schwieterman,
16 Division of Clinical Trials, CBER.

17 DR. HARRIS: I will ask that the mission
18 statement be read by Ms. Reedy.

19 Meeting Statement

20 MS. REEDY: Conflict of interest statement
21 for the Arthritis Advisory Committee on August 16,
22 2001.

23 The following announcement addresses
24 conflict of interest with regard to this meeting
25 and is made a part of the record to preclude even

1 the appearance of such at this meeting.

2 Based on the submitted agenda for the
3 meeting and all financial interests reported by the
4 committee participants, it is has been determined
5 that all interests in firms regulated by the Center
6 for Drug Evaluation and Research and the Center for
7 Biologics Evaluation and Research present no
8 potential for an appearance of a conflict of
9 interest at this meeting with the following
10 exception: In accordance with 18 United States
11 Code 208(b), a full waiver has been granted to Dr.
12 Kenneth Brandt. In addition, limited waivers have
13 been granted to Dr. Steven Abramson and Dr. Janet
14 Elashoff which allows them to participate in the
15 discussions without voting privileges.

16 Copies of these waiver statements may be
17 obtained by submitting a written request to the
18 Agency's Freedom of Information Office, Room
19 12A-30, Parklawn Building.

20 In addition, we would like to disclose for
21 the record that Dr. H. James Williams has an
22 interest which does not constitute financial
23 interest within the meaning of 18 United States
24 Code 208(a), but which could create the appearance
25 of a conflict. The Agency has determined,

1 notwithstanding this interest, that the interests
2 of the government in his participation outweighs
3 the concern that the integrity of the Agency's
4 programs and operations may be questioned.

5 In the event that the discussions involve
6 any other products or firms not already on the
7 agenda for which an FDA participant has a financial
8 interest, the participants are aware of the needs
9 to exclude themselves from such involvement, and
10 their exclusion will be noted for the record.

11 With respect to all other participants, we
12 ask in the interest of fairness that they address
13 any current or previous financial involvement with
14 any firm whose product they may wish to comment on.

15 DR. HARRIS: A welcome and introduction
16 from Dr. William Schwieterman.

17 Welcome and Introduction

18 DR. SCHWIETERMAN: Thank you, Dr. Harris.

19 I will keep my comments very short in the
20 interests of getting right to the data
21 presentations, but I would like to welcome the
22 committee and thank them for making time in their
23 August schedules for this meeting.

24 We look forward to a very interesting and
25 I think productive discussion about this new

1 molecular entity and possible treatment for
2 patients with rheumatoid arthritis, so thank you
3 all.

4 DR. HARRIS: Thank you.

5 We are going to go right into our
6 presentations. We will use the usual format in
7 that representatives of Amgen will first present
8 and then we will ask representatives of the FDA to
9 present after the break.

10 For Amgen, we have Dr. Perlmutter.

11 Amgen, Inc. Presentation

12 Overview

13 Roger Perlmutter, M.D., Ph.D.

14 DR. PERLMUTTER: Good morning. I am Roger
15 Perlmutter, Executive Vice President in charge of
16 Research and Development at Amgen.

17 [Slide.]

18 It is my privilege this morning to have
19 the opportunity to lead the Amgen team in our
20 presentation of anakinra, our interleukin-1
21 receptor antagonist for the treatment of rheumatoid
22 arthritis.

23 I should say that it is a special honor
24 for me to be leading this team since I have a long
25 interest in this field as a physician and as an

1 immunologist and former chair of the Department of
2 Immunology at the University of Washington.

3 I will provide a brief overview of how we
4 will proceed.

5 [Slide.]

6 We will begin with an overview. I will
7 describe the basic research aspects of anakinra. I
8 will speak also to our studies in preclinical
9 development and then I will ask Moraye Bear, lead
10 statistician in the program, to describe our
11 clinical experience with respect to efficacy.

12 Dr. Pirow Bekker will review the safety
13 experience with anakinra, and finally, we will call
14 on Dr. Stanley Cohen, a distinguished
15 rheumatologist from Dallas, Texas, with more than
16 two decades of experience in rheumatology practice
17 and in clinical trials, to give his perspective on
18 the therapeutic role of anakinra.

19 I will return at the end to provide a
20 brief wrap-up.

21 [Slide.]

22 Let me review our proposed indication for
23 anakinra. Anakinra is indicated for the reduction
24 in signs and symptoms of active rheumatoid
25 arthritis, in patients 18 years of age or older who

1 have failed one of more disease-modifying
2 antirheumatic drugs or DMARDs.

3 Anakinra can be used alone or in
4 combination with other DMARDs.

5 [Slide.]

6 To begin this review, let me try and place
7 the interleukin-1 receptor antagonist in the
8 context of our current understanding of
9 pro-inflammatory and anti-inflammatory cytokines,
10 which have an influence on the pathogenesis of
11 inflammatory arthritides.

12 It is well recognized at this point that
13 there exists a very large number of inflammatory
14 cytokines that mediate the process whereby white
15 blood cells gain access to the joint space and
16 ultimately result in destruction of the deformity
17 in the joint.

18 Chief among the pro-inflammatory
19 cytokines, as most of you are aware, are
20 interleukin-1 and TNF-alpha. It is of interest
21 that for both interleukin-1 and TNF-alpha, there
22 are natural anti-inflammatory agents which act
23 simultaneously, which has led to the view that
24 there exists a balance under normal circumstances
25 between pro-inflammatory and anti-inflammatory

1 signals.

2 For the case of TNF-alpha, soluble
3 versions of the TNF receptors circulate,
4 particularly p55-sTNF-RI, p75-sTNF-RI, and these
5 soluble receptors, of course, have been exploited
6 to develop agents that can be used in clinical
7 practice.

8 In the case of interleukin-1, which as I
9 will show you has a distinct spectrum of action,
10 the anti-inflammatory cytokine, if you will, or
11 anti-inflammatory agent, is an interleukin-1
12 receptor antagonist, and it is on this that our
13 attention will focus this morning.

14 [Slide.]

15 Now, interleukin-1 itself has a variety of
16 effects on normal cells. It activates monocytes
17 and macrophages as of course secreted mononuclear
18 cells, and that is involved in triggering both the
19 ability of these cells to release additional
20 inflammatory mediators, particularly products of
21 cyclooxygenase, but also to drive the movement of
22 these cells in the process of inflammation.

23 It acts on fibroblasts to cause collagen
24 deposition believed to be involved in synovial
25 pannus formation. It activates chondrocytes, which

1 are involved in cartilage breakdown through release
2 of a variety of proteases, some of which I will
3 have a chance to discuss. In addition,
4 interleukin-1 activates osteoclasts, which are
5 intimately involved in bone resorption.

6 [Slide.]

7 Now, evidence for the importance
8 interleukin-1 and TNF-alpha in the joint space has
9 accrued over many, many years, and I show here a
10 slide which is from a study published in 1989 in
11 which either interleukin-1 or TNF-alpha, the two
12 together are introduced into the joint space in the
13 rabbit knee.

14 You can see that if you have measure then
15 the total numbers of polymorphonuclear leukocytes,
16 shown in blue, or of monocytes, shown in red, that
17 the introduction of interleukin-1-alpha, in this
18 case in a 10-nanogram injection, or of TNF-alpha at
19 250 nanograms, results in some accumulation of
20 cells. The two together have a synergistic effect
21 in terms of both polymorphonuclear leukocyte
22 migration and also monocyte migration. I will
23 return to that effect a little bit later.

24 [Slide.]

25 Now, the evidence supporting the view that

1 interleukin-1, when introduced into the joint, can
2 drive the arthritic process, is I would say
3 overwhelming at this point, and I summarize some of
4 those studies on this slide, that repeated
5 intra-articular injections of interleukin-1 in the
6 rat cause arthritis, that continuous infusion of
7 IL-1 into the rabbit causes arthritis. The same
8 thing is true in mice.

9 But among these studies, perhaps the most
10 profound observation is the recent one published in
11 2000, that mice that lack the interleukin-1
12 receptor antagonist, that is, in those that have
13 sustained a gene disruption in the IL-1ra gene in
14 the mouse develops spontaneous arthritis.

15 This again is another piece of evidence
16 supporting the view that under normal
17 circumstances, there exists a balance between
18 pro-inflammatory and anti-inflammatory effects, and
19 of course fuels the speculation that the
20 introduction of interleukin-1 receptor antagonists
21 will shift that balance in favor of the
22 anti-inflammatory phenomenon.

23 [Slide.]

24 Now, interleukin-1 receptor antagonist is
25 itself a member of the interleukin-1 family. It is

1 structurally related to interleukin-1. It is
2 produced constitutively, as I have indicated, and
3 its production is augmented during inflammation.

4 It binds to interleukin-1 receptors and
5 occupies those receptors, but it does not activate
6 them, because it does not permit assembly of an
7 active receptor complex.

8 [Slide.]

9 In this sense, it is a pure receptor
10 antagonist, so diagrammatically, as I show you
11 here, an activated mononuclear cell will produce
12 interleukin-1 and interleukin-1 receptor
13 antagonists, whereas, interleukin-1, in binding to
14 its receptor, recruits the interleukin-1 receptor
15 accessory protein and other parts of the signaling
16 complex to result in activation and transcriptional
17 changes in the nucleus.

18 Interleukin-1 receptor antagonist binds to
19 the receptor, but does not permit assembly of the
20 signaling complex, and hence, activation is blocked
21 because by virtue of its occupancy of the receptor,
22 it does not permit interleukin-1 to gain access to
23 the receptor complex.

24 [Slide.]

25 Now, in order to test the possible utility

1 of interleukin-1 receptor antagonists, a general
2 model format has been used in which animals are
3 injected with something that stimulates an
4 arthritic response, and there are a variety of
5 these kinds of models involving immune responses
6 directed, for example, against type 2 collagen or
7 adjuvant mycobacterial immunization, a whole
8 variety of these things over a period of a week
9 will cause arthritis to develop in these
10 experimental species.

11 Introduction of anakinra can then affect
12 the arthritic process, and this is followed over a
13 period of one to two weeks, and I will show you
14 some of those data based on studies primarily of
15 histology, but also using bone markers and x-ray
16 scanning.

17 [Slide.]

18 Here is an example in a collagen-induced
19 arthritis model, looking at treatment effects of
20 anakinra on inflammation. You can see in this
21 experiment we are measuring day of arthritis on the
22 abscissa. On the ordinate, you can see the mean
23 ankle joint diameter, so we are following joint
24 swelling as an index of inflammation. When vehicle
25 control is provided, there is this monotonic

1 increase in joint swelling, reflecting the progress
2 of the arthritic process.

3 On the other hand, if anakinra is provided
4 at continuous infusion via a pump, at 0.04
5 mg/kg/hr, 0.2, 1, and 5, you can see this uniform
6 response, that is, to first approximation dose
7 proportional. As you increase the dose of
8 anakinra, you block the inflammatory process.

9 [Slide.]

10 You can follow this, not only for joint
11 swelling, but also for a variety of other features
12 of the inflammation process. So, here we are
13 looking at cellularity, we are looking at the
14 histologic score with respect to cartilage, and
15 again on the abscissa, the increasing dose of
16 anakinra and a score in this case from zero to 4
17 for these events, again, for pannus accumulation in
18 the arthritic joint, and for bone damage itself.
19 These are all judged histologically.

20 You can see that anakinra affects all of
21 these processes, and does so at a similar dose in
22 this experimental model.

23 [Slide.]

24 Now, when we think about the arthritic
25 process, as I have indicated, there are multiple

1 cytokines that are active within the joint space.
2 The principal cytokines towards which attention has
3 been directed most recently, of course, are
4 TNF-alpha and, as I have indicated, interleukin-1.

5 You might imagine because TNF-alpha and
6 interleukin-1 affect the release of each other,
7 that they would behave in much the same way, but,
8 in fact, a variety of studies demonstrate that each
9 one has a unique spectrum of action, and that is an
10 important feature of our thinking in introducing
11 interleukin-1 receptor antagonists as an
12 anti-inflammatory drug for rheumatoid arthritis.

13 [Slide.]

14 In this slide, I am showing you the effect
15 on human chondrocytes in vitro of interleukin-1 or
16 TNF-alpha which is provided to these cells at doses
17 which you can see on the abscissa that range from
18 none, the control, up to, in this case, 12,500
19 picomolar or 12.5 nanomolar.

20 What we are following here is the release
21 of matrix metalloproteinase 3, one of a set of
22 proteinases that is released by chondrocytes and
23 that are intimately involved in cartilage
24 destruction.

25 As you can see, the introduction of

1 interleukin-1 causes a dramatic increase in the
2 release of matrix metalloproteinase, whereas, there
3 is very little release that is catalyzed by the
4 introduction of TNF-alpha even at quite high
5 concentrations, in this case 50 nanomolar.

6 So, despite the fact that the TNF receptor
7 is occupied, there is no significant release of
8 matrix metalloproteinase 3, just an index of the
9 difference between these two molecules.

10 [Slide.]

11 Similarly, now summarizing over a variety
12 of experiments that have been performed in the
13 mouse, in the rat, and in rabbit with streptococcal
14 cell wall induced arthritis or flare with
15 antigen-induced arthritis, collagen-induced
16 arthritis, immune complex arthritis, in all of
17 these cases, early inflammation to a first
18 approximation is mediated by both TNF and IL-1, and
19 these are experiments that are performed using
20 blocking antibodies as a means to try and
21 antagonize the effects of these two cytokines.

22 In contrast, if one examines the erosive
23 features of this arthritis, whereas, antibodies
24 directed against interleukin-1 will block these
25 effects routinely, it is very rare for antibodies

1 directed against TNF to have this effect, just
2 another representation of the fact that TNF and
3 interleukin-1 have different effects on the joint.

4 [Slide.]

5 This, of course, inspires a different kind
6 of experiment analogous to the one that I showed
7 you before in which interleukin-1 and TNF are
8 introduced either alone or together into the
9 rabbit.

10 In this case, looking again at a
11 collagen-induced arthritis model in Lewis rats
12 where an attempt is made to block the arthritic
13 process using either anakinra interleukin-1
14 receptor antagonists or a soluble version of TNF
15 receptor, the sTNF-RI, you can see that either one
16 of these significantly blocks features of the
17 inflammatory process.

18 We are measuring here inflammation,
19 pannus, cartilage damage, or bone resorption, as I
20 have shown you before. However, when the two are
21 provided together with anakinra at 100 mg/kg and
22 sTNF-RI at 3 mg/kg, there is a dramatic synergistic
23 effect which has been seen in several studies.

24 [Slide.]

25 So, with respect to interleukin-1 receptor

1 antagonists then, there is a wealth of preclinical
2 data that suggests both that interleukin-1 is
3 intimately involved in the pathogenesis of
4 inflammatory arthritides and also that
5 interleukin-1 receptor antagonists could be used to
6 block this effect.

7 The interleukin-1 receptor antagonist was
8 identified at the genetic level in 1990, and the
9 initial recombinant DNA manufacturing process was
10 reduced to practice in the same year. The drug
11 substance is a recombinant protein of 153 amino
12 acids, differing from native interleukin-1 receptor
13 antagonists by virtue of its N-methionyl
14 derivatization. It is 17.3 kilodaltons in length,
15 and in the final dosage form is a daily injectable
16 at 100 mg, fixed dose, in prefilled syringes.

17 [Slide.]

18 I will just summarize very briefly the
19 preclinical experience with respect to safety
20 toxicology. The toxicity of anakinra has been
21 studied in rats and macaques over a long duration
22 because of the fact that interleukin-1 receptor
23 antagonist is closely conserved across species, no
24 neutralizing antibodies were observed in studies up
25 to six- month duration, and hence, it was possible

1 to perform these studies over long term in these
2 preclinical species.

3 The safety margins exceeded 90-fold in
4 rats based on exposure and 30-fold in monkeys for
5 AUC. Anakinra was studied alone and in combination
6 with methotrexate, and also it has been studied
7 with TNF inhibitors.

8 The animal studies revealed injection site
9 inflammation, but no other target organ toxicity at
10 any dose.

11 [Slide.]

12 With respect to the pharmacokinetic
13 profile of anakinra, I show you this one slide,
14 which is PK profiles in RA patients after a single
15 administration subcutaneously of anakinra at doses
16 from 0.5 mg/kg to 6 mg/kg. I think that you can
17 see that the accumulation is dose linear for the
18 single dose experiment.

19 Half lives from a variety of different
20 studies have been calculated at about six hours in
21 rheumatoid arthritis patients for anakinra. These
22 data support the daily injectable paradigm that we
23 have articulated.

24 [Slide.]

25 Now, let me speak very briefly to the

1 process whereby we came to be before you this
2 morning. The regulatory submissions for anakinra
3 began with the license application in December of
4 1999, that included three studies - 0560, 960180,
5 and 960182. These provided the basis for the
6 selected dose of 100 mg/day.

7 As part of the feature of the evolution of
8 this application, two additional studies which will
9 be described this morning, 990145 and 990757, our
10 large safety study, were performed, and 990145, as
11 part of a discussion with the FDA, is a long-term
12 study with a prespecified six-month efficacy
13 evaluation point, which will be described in
14 detail.

15 On the basis of these studies, in March of
16 2001, a complete response letter was received, and
17 we now have an FDA Advisory Committee for which we
18 are grateful.

19 [Slide.]

20 I want to emphasize that we have enormous
21 clinical experience with anakinra. In total, there
22 are 2,332 patients who have been studied in
23 randomized, placebo-controlled studies and
24 extensions, and have received at least one dose of
25 anakinra. There are 2,606 patients through all the

1 studies who have received at least one dose.

2 [Slide.]

3 These numbers underestimate the true
4 exposure because, of course, what is interesting is
5 how much anakinra and over what period.

6 If we focus only on those individuals who
7 have received the requested dose of 100 mg or more,
8 1,379 patients have received this dose for a period
9 of greater or equal in six months, and 237
10 individuals for more than a year, and as you can
11 see, we have some individuals who have been
12 receiving this drug for as long as five years, so
13 there is substantial clinical exposure, substantial
14 clinical experience, and it is upon this experience
15 that we base our application this morning for
16 anakinra for the treatment of rheumatoid arthritis.

17 [Slide.]

18 With that, I am going to turn the podium
19 over to Moraye Bear, our lead statistician in the
20 anakinra program, and she will describe the
21 clinical efficacy results for you in great detail.

22 Thank you.

23 Clinical Experience

24 Moraye Bear, M.S., M.A.

25 MS. BEAR: Good morning. My name is

1 Moraye Bear. I am the clinical team leader for
2 anakinra.

3 This morning, Dr. Bekker and myself will
4 be reviewing the clinical trial data from these
5 five randomized, placebo-controlled studies that
6 represent the clinical experience of over 2,900
7 patients.

8 I will be presenting the efficacy data
9 from the first four trials, and Dr. Bekker will be
10 reviewing the safety data across all five studies
11 including our very large safety study 990757.

12 [Slide.]

13 My review of the efficacy data this
14 morning will begin with our earlier RA efficacy
15 studies, study 0560, 960182, and 960180, where we
16 were able to, in fact, establish the efficacy of
17 anakinra reducing the signs and symptoms of RA,
18 most notably at the higher anakinra dose range.

19 As Dr. Perlmutter noted, from clinical
20 review of both the efficacy and the safety data
21 from these earlier trials, we selected a dose of
22 100 mg/day to bring forward into our large
23 confirmatory study 990145. As I review those data,
24 we will see that we were, in fact, able to confirm
25 the efficacy of anakinra in reducing the signs and

1 symptoms of RA using our proposed dose of 100
2 mg/day.

3 [Slide.]

4 I would like to begin by briefly reviewing
5 the types of patients that have participated in
6 these studies, beginning with the patient
7 disposition. We see an aggregate for both placebo
8 and anakinra-treated patients, the disposition here
9 for all five trials.

10 The first thing we notice is that, in
11 fact, the majority of patients that were randomized
12 did, in fact, go on to receive study drug, and that
13 we have about a 75 percent completion rate. We
14 notice a slightly higher completion rate in study
15 960182, as this was a 12-week study.

16 The most common reason cited for early
17 withdrawal is adverse events, and except for
18 injection site reactions, this reason for
19 withdrawal was well balanced between placebo and
20 anakinra-treated patients within each of the five
21 trials.

22 Withdrawal due to lack of efficacy was
23 slightly higher among placebo patients, and you
24 will notice that there were no withdrawals due to
25 deaths except in our very large safety study

1 990757, where the withdrawal due to death rates
2 were again equivalent between placebo and
3 anakinra-treated patients.

4 [Slide.]

5 The baseline demographics were well
6 balanced among placebo and anakinra groups within
7 each of the trials and very typical of what we
8 would expect to see in an RA study. The majority
9 of patients were female, on average about 55 years
10 of age, weighing about 75 kilograms at entry.

11 Notice that the majority of patients were
12 Caucasian especially in our two European studies,
13 study 0560 and study 960182.

14 [Slide.]

15 With respect to disease status, we can see
16 that clearly the patients participating in these
17 studies had evidence of active RA. There is some
18 variability among the trials and that is reflecting
19 the various inclusion and exclusion criteria of
20 these studies, but we can see that on average, the
21 duration of RA ranged from 3 1/2 years to 10-plus
22 years. Tender/painful joint counts ranged from 20
23 to approximately 35, swollen joint counts from 20
24 to 25.

25 Clear evidence of physical disability is

1 reflected by the HAQ, and elevated acute phase
2 reactants reflected by CRP and ESR. Baseline RA
3 meds are depicted on this slide. We see that
4 approximately half of the patients were taking
5 corticosteroids at study entry with approximately
6 70 to 85 percent of patients on NSAIDs.

7 In terms of patients being on
8 methotrexate, we notice that all patients were on
9 methotrexate in our 960180 and 990145 studies as
10 those were methotrexate combination studies, so
11 patients were required to be on background
12 methotrexate. However, in studies 0560 and 960182,
13 patients were not permitted to be on any DMARD.

14 If we look in the last column with our
15 safety study 990757, we see that patients were
16 permitted to be on methotrexate alone, methotrexate
17 in combination with other DMARDs, or various
18 combinations of DMARDs on top of the anakinra that
19 they were receiving.

20 [Slide.]

21 I will begin my review of the efficacy
22 data starting with our monotherapy study, study
23 0560.

24 [Slide.]

25 This was a randomized, double-blind,

1 placebo-controlled trial and patients were
2 randomized in equal allocation to one of four
3 treatment groups, either placebo, 30, 75, or 150
4 mg/day. In this study, as in all the studies that
5 I will be presenting, study drug was administered
6 as a daily sub-Q injection.

7 As noted earlier, the most notable entry
8 criteria of this trial was that patients were not
9 permitted to be on any background DMARD, and this
10 included methotrexate.

11 There were 472 patients, it was a 24-week
12 trial conducted in Europe, and the prespecified
13 endpoint was the ACR20 at week 24. We will notice
14 that an important secondary endpoint in this trial
15 was the change from baseline at week 24 with
16 respect to the Larsen score. As you know, this is
17 a measurement reflective of radiographic disease
18 progression.

19 [Slide.]

20 The results of the primary endpoint for
21 study 0560 are depicted here with the proportion of
22 ACR20 responders at week 24 noted on the vertical
23 axis and the treatment groups on the horizontal
24 axis.

25 I want to point out that the prespecified

1 evaluatable subset in this study was a modified
2 Intent to Treat subset, which meant that patients
3 had to receive at least one dose of study drug and,
4 in addition, had to have at least one post-baseline
5 measurement.

6 The prespecified method of imputation was
7 the last observation carried forward, and what we
8 notice is that clearly, anakinra-treated patients
9 are achieving ACR20 responses at week 24 at a
10 higher rate than placebo patients with statistical
11 significance noted at the 30, and the highest
12 anakinra dose group, the 150 mg dose group, where
13 43 percent of anakinra-treated patients achieved an
14 ACR20 response at week 24.

15 [Slide.]

16 Examining the ACR20 response across the
17 various time points indicates that the effects of
18 anakinra occurred quite rapidly beginning as early
19 as week 2 and were maintained throughout the
20 treatment period.

21 [Slide.]

22 Examination of the individual ACR
23 components reveal effects that are very supportive
24 of what we saw in the composite score. The effects
25 of a anakinra occurred early on were maintained

1 throughout the treatment period and most notably
2 again at the 150 mg dose group, and I will point
3 out that at week 24, which was the prespecified
4 time point, the 150 mg dose group was statistically
5 different from placebo in each of the ACR
6 components depicted here, as well as morning
7 stiffness.

8 [Slide.]

9 In summary, study 0560 established the
10 efficacy of anakinra in reducing the signs and
11 symptoms of RA in a monotherapy setting.

12 [Slide.]

13 The next study I will be describing is
14 study 960182, and this was a study designed to
15 examine the lower end of the anakinra dose range.

16 [Slide.]

17 It, too, was a randomized, double-blind,
18 placebo-controlled study. Patients were randomized
19 to receive either placebo, 2.5, 10, or 30 mg/day.
20 Like the previous study, patients were not
21 permitted to be on any background DMARD, and this,
22 of course, included methotrexate.

23 There were 141 patients in this trial. It
24 was of 12-week duration, conducted in Europe, and
25 the prespecified primary endpoint was the ACR20 at

1 week 12.

2 [Slide.]

3 For this study, the prespecified evaluable
4 subset was the Intent to Treat subset, and this was
5 all patients randomized who received at least one
6 dose of study drug, and the prespecified method for
7 missing data was a nonresponder imputation, which
8 meant if a patient was missing an ACR composite
9 score, they were categorized as a treatment failure
10 or a nonresponder.

11 We see the results that at these doses,
12 none of the anakinra groups achieved either
13 numerical or statistical superiority to placebo.

14 [Slide.]

15 Our conclusion from study 960182, then,
16 would suggest that doses of 30 mg or less were not
17 effective in reducing the signs and symptoms of RA,
18 although we do need to temper that conclusion with
19 the fact that we did have small sample sizes and a
20 greater than expected placebo response rate.

21 [Slide.]

22 Study 960180 was our first study exploring
23 anakinra in combination with methotrexate.

24 [Slide.]

25 This was a randomized, double-blind,

1 placebo-controlled trial. Patients were randomized
2 to one of six treatment groups denoted here.
3 Dosing was on a mg/kg basis, and as mentioned,
4 patients were required to be on stable doses of
5 methotrexate throughout the study of 15 to 25
6 mg/week.

7 There were 419 patients participating in
8 the study. It was originally of 12-week duration,
9 later amended before any blind reg to be a 24-week
10 study, and at the same time, we added the two doses
11 highlighted in yellow, the 0.04 and 1.0 mg/kg dose
12 group.

13 The study was conducted in North America
14 and Australia. The prespecified primary endpoint
15 was the ACR20 at week 12, and we, of course, will
16 be showing you those results at week 24.

17 [Slide.]

18 We see here the results for the primary
19 endpoint, the ACR20 at week 12. The primary
20 analysis of this endpoint was a single test of dose
21 response that was conducted across all six
22 treatment groups simultaneously, and those results
23 depicted here indicate a very highly significant
24 dose response of p equals 0.001, indicating that
25 higher ACR20 response rates were associated with

1 higher anakinra doses.

2 Following the significance of this overall
3 omnibus test, we then conducted individual pairwise
4 comparisons and were able to detect statistical
5 significance at the 0.1 and the two higher anakinra
6 dose groups of 1.0 and 2.0 mg/kg/day.

7 [Slide.]

8 The results at week 24 are very similar to
9 what we observed at week 12, a highly significant
10 dose response with statistical significance
11 achieved at the 1.0 mg/kg dose group.

12 [Slide.]

13 Examination of the ACR20 responses over
14 time reveal an early onset of action observed at
15 approximately week 4, that is maintained throughout
16 the treatment period. I have shown you just the
17 top three anakinra doses in this slide. We do have
18 I believe these results for all of the doses in
19 your briefing packet.

20 [Slide.]

21 In addition to looking at the ACR20
22 response at just week 24, keeping with the FDA
23 guidelines, we wanted to examine the ability of
24 anakinra to enable patients to maintain or sustain
25 those benefits throughout the treatment period.

1 We defined a sustained responder as a
2 patient who achieved an ACR20 response for at least
3 four out of the six monthly measurements with the
4 caveat that at least one of those measurements had
5 to be at week 12 or 24, and those results are
6 depicted here, again, a significant dose response
7 with statistical significance at the two higher
8 anakinra dose groups, the 1.0 and 2.0 mg/kg groups,
9 where patients were twice as likely to achieve a
10 sustained benefit in comparison to placebo
11 patients.

12 [Slide.]

13 We also examined the ability of
14 anakinra-treated patients to achieve higher
15 magnitudes of response reflected in the ACR50 and
16 the ACR70 responses. Those data are depicted in
17 this histogram. Again, we see a highly significant
18 dose response.

19 Higher magnitudes of improvement are
20 associated with higher doses of anakinra, and I
21 want to bring your attention to the 1.0 mg/kg dose
22 group where one in four anakinra-treated patients
23 achieved an ACR50 response, and one in 10 achieved
24 an ACR70 response.

25 [Slide.]

1 These are the individual ACR components.
2 Again, I have just displayed here the top three
3 doses. You have the full dose range in the
4 briefing packet, but we see an early onset of
5 action that is maintained throughout the treatment
6 period and that these effects are generally seen in
7 the higher anakinra dose groups of 1.0 and 2.0
8 mg/kg/day.

9 [Slide.]

10 In summary, study 960180 established the
11 efficacy of anakinra in reducing the signs and
12 symptoms of RA in a methotrexate combination study.

13 [Slide.]

14 I will now move on to our large
15 confirmatory study 990145. If you recall, we
16 examined the earlier studies in terms of the
17 efficacy and safety, and prospectively chose a dose
18 of 100 mg/day to bring into this study.

19 [Slide.]

20 It was a randomized, double-blind,
21 placebo-controlled trial. Patients were randomized
22 in equal allocation to receive either placebo or
23 100 mg/day of anakinra. Like the previous study,
24 patients were required to be on stable doses of
25 background methotrexate between 10 and 25 mg/week.

1 There are 906 patients participating in
2 this study. It is of 52-week duration. The
3 double-blind period is 52-week duration. There is
4 an open label that extends out for another 2 1/2
5 years.

6 It is being conducted in North America and
7 Australia, and the prespecified primary endpoint in
8 this study is the change from baseline at week 52
9 with respect to the modified Sharp total score.

10 That data remains blinded, however, as Dr.
11 Perlmutter indicated, in an effort to provide
12 additional signs and symptoms data to the Agency,
13 we conducted an analysis of the ACR20 responses at
14 week 24 for the first 501 patients receiving study
15 drug.

16 [Slide.]

17 Those results depicted here indicate that
18 anakinra patients are more likely to achieve an
19 ACR20 response using a proposed dose of 100 mg/day
20 in comparison to placebo where 38 percent of
21 anakinra-treated patients achieved an ACR20
22 response compared to only 22 percent of the placebo
23 patients with a p less than 0.001.

24 [Slide.]

25 These responses were achieved early and

1 were maintained throughout the entire treatment
2 period with anakinra-treated patients achieving
3 both clinical and statistical differences from
4 placebo at each of the time points examined.

5 [Slide.]

6 Looking at the sustained response,
7 anakinra-treated patients were more than twice as
8 likely to sustain these benefits throughout the
9 treatment period compared to placebo patients.

10 [Slide.]

11 In terms of the magnitude of response,
12 anakinra-treated patients were more than twice as
13 likely to achieve an ACR50 response, and three
14 times more likely than placebo patients to achieve
15 an ACR70 response, both statistically significant
16 from placebo patients.

17 [Slide.]

18 Examination of the individual ACR
19 components also reveals an effect of anakinra,
20 supporting what we saw for the overall composite
21 score, early effects that are maintained throughout
22 the treatment period.

23 At week 24, the prespecified time point,
24 anakinra-treated patients were more likely, both
25 clinically and statistically, to achieve benefits

1 over placebo patients at each of these ACR
2 components with the exception of swollen joint
3 counts where at week 24, there was no difference
4 between the two groups, however, upon review of the
5 differences across the entire treatment period, we
6 do see that, in general, anakinra-treated patients
7 tended to do better than placebo.

8 [Slide.]

9 So, in summary, study 990145, our
10 confirmatory efficacy study of over 500 patients
11 confirmed the efficacy of anakinra in reducing the
12 signs and symptoms of RA. We confirmed the ACR20
13 responses at week 24, the early onset of action,
14 the sustained response and the ability of
15 anakinra-treated patients at our proposed dose to
16 achieve higher magnitudes of response, and this was
17 strongly supported by what we saw in each of the
18 individual ACR components.

19 [Slide.]

20 Now, I would like to move on to the
21 radiographic data. If you recall, in 0560, I
22 mentioned that one of the important secondary
23 endpoints in that study was the Larsen score, a
24 radiographic endpoint.

25 [Slide.]

1 The radiographs in 0560 were reviewed
2 using two different scoring methods. The first
3 method, the Larsen score, was the prespecified
4 method. This is a scoring system that is more
5 heavily weighted towards erosions.

6 We subsequently had these radiographs
7 rescored using a Genant modified Sharp score as the
8 literature at the time seemed to suggest that the
9 Sharp score would be more sensitive in that it not
10 only had erosion measurement, but in addition, it
11 also measured very specifically joint space
12 narrowing. I will be showing you the results of
13 both of these scores.

14 [Slide.]

15 On the lefthand panel is the change from
16 baseline at week 24 for the Larsen score, the
17 righthand panel depicts the Sharp total score.
18 Higher change from baseline scores denote
19 increasing disease progression. We see that the
20 anakinra-treated patients are clearly doing better
21 than placebo patients, representing about a 40
22 percent or more decrease in the rate of progression
23 compared to placebo.

24 None of the individual dose groups for the
25 Larsen score achieved statistical significance,

1 however, for the modified Sharp total score, we
2 were also able to achieve statistical significance
3 for the individual dose groups, as well.

4 [Slide.]

5 These histograms depict the two sub-scales
6 of the Sharp score, the joint space narrowing and
7 the erosion sub-scale. Again, we see the effects
8 very clearly here of anakinra in being able to
9 reduce disease progression over this 24-week
10 treatment period.

11 [Slide.]

12 Now, in addition to reviewing the effects
13 of anakinra on radiographic disease progression
14 over 24 weeks, we also had the opportunity to
15 examine this over a 48-week treatment period by
16 looking at the data in our extension study 564.

17 [Slide.]

18 Patients who completed study 0560 were
19 eligible to roll over into an extension study 0564
20 where all patients received treatment with
21 anakinra. Placebo patients were simply
22 re-randomized to one of the three anakinra dose
23 groups, and patients originally randomized to
24 anakinra were simply maintained on their original
25 randomized treatment.

1 I want to point out that in study 564, it
2 was double-blind, so even though patients knew they
3 were receiving treatment with anakinra, they didn't
4 know what dose they were receiving, nor did they
5 know what dose or treatment they had received
6 previously in study 0560.

7 [Slide.]

8 The results of the modified Sharp total
9 score and the Larsen score depicted here is change
10 from baseline at week 24 and week 48, and the week
11 48 time point we can see that patients treated with
12 anakinra for the full 48 weeks are doing better
13 than the cohort of placebo patients even though
14 these placebo patients had now been receiving
15 active treatment with anakinra for the last 24
16 weeks.

17 We don't see statistical significance for
18 the Larsen score, but we are able to detect
19 statistical significance for the modified Sharp
20 total score.

21 [Slide.]

22 The results in the two sub-scales for the
23 Sharp score joint space narrowing and erosion,
24 again very similar, showing a benefit of anakinra
25 treatment.

1 [Slide.]

2 In summary, we have shown that anakinra is
3 effective in reducing the signs and symptoms of RA
4 in three independent trials, 0560, 960180, and our
5 large study 990145 with over 500 patients.

6 We have shown this in a monotherapy
7 setting, and we have also shown this in a
8 methotrexate combination setting. The results are
9 robust, and they are consistent.

10 In addition, we have also shown that
11 anakinra has effects on radiographic disease
12 progression as measured by two different scoring
13 systems, both the Larsen and the modified Sharp
14 score.

15 [Slide.]

16 I would like to turn the podium over now
17 to Dr. Bekker.

18 [Slide.]

19 Pirow Bekker, M.D., Ph.D.

20 DR. BEKKER: Good morning. My name is
21 Pirow Bekker. I am Senior Director of Clinical
22 Research at Amgen. I will be presenting the safety
23 data with anakinra and the treatment of patients
24 with rheumatoid arthritis.

25 [Slide.]

1 Five randomized, double-blind,
2 placebo-controlled trials have been conducted with
3 anakinra in the treatment of patients with
4 rheumatoid arthritis, and those five studies are
5 shown here. That represents 91 percent of all
6 patients studies with anakinra.

7 Firstly, the large confirmatory efficacy
8 study, which was discussed by Moraye Bear;
9 secondly, a large safety study including more than
10 1,000 patients receiving anakinra at the
11 recommended clinical dose of 100 mg; and then three
12 other studies as shown here.

13 [Slide.]

14 In addition, five pharmacokinetic and
15 supportive studies were also conducted with
16 anakinra, and those studies are shown here. It
17 includes a single-dose pharmacokinetic study, a
18 multi-dose PK study, two continuous infusion
19 studies, and then one dose and frequency study.

20 [Slide.]

21 There were also eight extension studies,
22 four of these for the monotherapy study, and then
23 one each for the methotrexate combination study,
24 low-dose monotherapy study, multi-dose, PK, and the
25 dose and frequency study.

1 [Slide.]

2 As Dr. Perlmutter mentioned in his
3 opening, Amgen has an extensive experience with
4 anakinra in the treatment of patients with this
5 disease. More than 2,300 patients have received at
6 least one dose of anakinra in the randomized,
7 placebo-controlled studies and their extensions,
8 and when you include all patients from all studies
9 in RA, more than 2,600 patients have received at
10 least one dose.

11 [Slide.]

12 Now, in order to analyze the safety data,
13 we decided to combine data across all five
14 randomized, placebo-controlled trials and to group
15 patients into their respective treatments - placebo
16 patients receiving less 100 mg anakinra, those
17 receiving 100 mg, which is the recommended clinical
18 dose, those receiving greater than 100 mg anakinra,
19 and then also what I will be including in
20 subsequent slide, is an all anakinra group, which
21 includes patients across all three anakinra groups.

22 As noted in this slide, 845 patient years
23 of anakinra exposure have been accumulated in these
24 five randomized, placebo-controlled trials, 66
25 percent of which had been at the recommended

1 clinical dose or for 100 mg.

2 Notice that when you combine data from all
3 RA studies, we have 1,873 patient years of
4 exposure. Also shown here is the median patient
5 exposure expressed in weeks, and you can see this
6 is very similar across groups at approximately 24
7 weeks.

8 In subsequent slides, I will be showing
9 the analysis for the adverse events in terms of
10 accrued incidence of adverse events, and you can
11 see that would be appropriate since the exposure
12 across groups was similar.

13 [Slide.]

14 Now, the points of discussion today
15 include firstly a discussion of the overall adverse
16 event profile. This includes a discussion of
17 deaths observed in the studies, malignancies, other
18 serious adverse events, and withdrawals due to
19 adverse events.

20 Secondly, injection site reactions, I will
21 also briefly discuss anti-anakinra antibodies, and
22 then the FDA has posed a number of questions to the
23 advisory panel for discussion today, and the
24 remainder of my presentation will focus on these
25 topics.

1 Firstly, infections including serious
2 infections; white blood cell profile including a
3 discussion of the neutrophil profile, Amgen has
4 done an anakinra/etanercept combination study, and
5 then lastly, there is also an ongoing pediatric
6 study in patients with juvenile rheumatoid
7 arthritis.

8 [Slide.]

9 With regard to the safety overview across
10 these five randomized, placebo-controlled trials,
11 when you look at the incidence of patients
12 experiencing any adverse event, the incidence was
13 85 percent in the placebo group, 91.7 percent in
14 the 100 mg anakinra group.

15 We noticed a slight increase as the dose
16 of anakinra was increased. We also noticed in the
17 review of our data that patients experiencing
18 injection site reaction were more commonly seen in
19 the anakinra groups compared to placebo, so we also
20 did an analysis excluding injection site reactions,
21 and you can see that the incidence in this case is
22 very similar across groups.

23 With regard to serious adverse events,
24 this is the regulatory definition of serious and
25 mostly represent hospitalization due to adverse

1 events. The incidence was 6.5 percent in placebo,
2 7.1 percent in the 100 mg anakinra group, somewhat
3 higher in the greater than 100 mg anakinra group
4 and I will be discussing that in more detail
5 subsequently.

6 With regard to deaths in these studies,
7 there was one death in the placebo group due to
8 myocardial infarction, one death in the less than
9 100 mg anakinra group due to small cell lung
10 cancer, four deaths in the 100 mg anakinra group,
11 one due to worsening pulmonary fibrosis in a
12 patient on long-standing methotrexate therapy, one
13 death due to suicide in a patient with a history of
14 depression, one death due to gastrointestinal
15 hemorrhage in a patient with a history of GI
16 ulcerative disease, and then in the fourth case,
17 this was due to metastatic melanoma in a patient
18 with a history of melanoma at baseline.

19 There was one death in the greater than
20 100 mg anakinra group, and this was due to
21 cerebrovascular accident. I should also point out
22 that there was one death in the confirmatory
23 efficacy study. This was due to pulmonary fibrosis
24 worsening again in a patient with long-standing
25 methotrexate use.

1 With regard to withdrawals due to adverse
2 events, the incidence was 11.6 percent in placebo,
3 13.6 percent in the 100 mg anakinra group.

4 [Slide.]

5 If we look firstly at deaths observed,
6 there were 19 subjects who died during the anakinra
7 studies. What I am showing in this table is a
8 breakdown by study.

9 For the monotherapy study in which
10 patients were randomized in a 3 to 1 ratio,
11 anakinra to placebo, there were three deaths in the
12 anakinra group. All three of those deaths occurred
13 after patients have discontinued study drug, two of
14 these cases for three months or greater.

15 In the methotrexate combination study and
16 the low dose monotherapy study, we did not see any
17 deaths.

18 In the safety study, the incidence was the
19 same, at 0.4 percent since the randomization ratio
20 again was 4 to 1, anakinra to placebo.

21 In the confirmatory efficacy study, there
22 was one death, incidence of 0.2.

23 In the uncontrolled extension studies in
24 which patients were receiving only anakinra, and
25 there was no placebo-controlled group, there were

1 10 deaths, an incidence of 1.1 percent.

2 [Slide.]

3 So, if we look at the most frequently
4 reported serious adverse events, those that
5 reported an incidence of 0.2 percent or greater,
6 the incidence was 6.5 in placebo, 7.1 percent in
7 the 100 mg anakinra group, and 12.2 percent in the
8 greater than 100 mg anakinra group.

9 Upon closer examination of the cases in
10 the greater than 100 mg anakinra group, we noticed
11 that there was no clustering of adverse events
12 around particular terms, but that these were spread
13 across a number of unrelated terms, for example,
14 there were two patients with arthralgia who were
15 hospitalized and treated for that.

16 There were two cases of repair of inguinal
17 hernia, patients hospitalized for that, and they
18 are not shown in this slide, there were also two
19 cases of tendon rupture, which was associated with
20 the rheumatoid arthritis disease process, and was
21 not considered to be related to study drug.

22 With regard to abdominal pain, the
23 incidence was similar across groups, and then in
24 terms of dyspnea, there was one case in the less
25 than 100 gm anakinra group. This was in a patient

1 who had worsening of chronic obstructive pulmonary
2 disease, and then four patients in the 100 mg
3 anakinra group, two of these were associated with
4 pneumonia and two others with worsening pulmonary
5 fibrosis.

6 [Slide.]

7 With regard to malignancies, we observed a
8 total number of 30 cases of malignancies over the
9 course of these studies, and this includes all of
10 the RA studies conducted.

11 I am showing 27 of those in this table, 6
12 in placebo, 21 in anakinra, and excluding two
13 cancers, which were recurring cancers, two of
14 these. One was bladder cancer and the other one
15 was melanoma. There is also one case of prostate
16 cancer which is in the blinded ongoing study.

17 So, in this table, I am showing the number
18 of malignancies, as well as the rate per 100
19 patient years. The reason why I am showing the
20 data in terms of rate, and not accrued incidence
21 here, is because the anakinra exposure in total was
22 6.3 times higher than in the placebo group.

23 So, with regard to the rate of any
24 malignancy, you can see that, if anything, it was
25 somewhat higher in the placebo group versus

1 anakinra.

2 There were six cases of breast cancer.
3 Two of these were breast carcinoma in situ. You
4 can see similar incidence as we go down the list.
5 I want to point out since lymphoproliferative
6 cancers occur more commonly in patients with
7 rheumatoid arthritis, in terms of non-Hodgkin's
8 lymphoma, there was one case in the anakinra group.
9 This was in a patient with a suspicious
10 post-auricular lymph node biopsy pre-study, and
11 then there was one case of Hodgkin's lymphoma in
12 the placebo group.

13 [Slide.]

14 We also wanted to compare the observed
15 number of malignancies to the expected number based
16 on the National Cancer Institute's Surveillance
17 Epidemiology and End Results statistics.

18 From the 21 cases of malignancies that I
19 have shown you in the previous slide, we excluded
20 two cases of breast carcinoma in situ and four
21 cases of basal cell carcinoma since those are not
22 included in the SEER statistics.

23 We added back the one case of prostate
24 cancer, which remains blinded, to be conservative.
25 You can see here that the total number of

1 malignancies observed is very similar to the number
2 expected. We didn't see any cases of leukemia,
3 there was one case of non-Hodgkin's lymphoma,
4 expected 0.58, and then with regard to the
5 by-gender distribution of these malignancies, the
6 observed number was very similar to the expected
7 number.

8 [Slide.]

9 With regard to withdrawals due to adverse
10 events, those most common reasons for withdrawal,
11 this was 11.6 percent in placebo, 13.6 percent in
12 the 100 mg anakinra group, the most common reason
13 for withdrawal was injection site reaction, which
14 occurred an incidence of 5.6 percent in anakinra
15 group versus 1.3 in placebo.

16 Worsening of rheumatoid arthritis or
17 arthralgia occurred more commonly in the placebo
18 group versus the anakinra groups, and this finding
19 was consistent with the efficacy findings presented
20 earlier.

21 Headache and abdominal pain occurred at a
22 similar incidence across groups.

23 [Slide.]

24 Regarding injection site reactions, the
25 incidence in the placebo group was 26.9 percent,

1 and it was increased in the anakinra groups. This
2 appeared to be dose related. I want to emphasize,
3 though, that the majority of these injection site
4 reactions, 95 percent was considered to be mild or
5 moderate by the investigators.

6 The most common manifestations of
7 injection site reactions were erythema, pruritus,
8 rash, pain, and/or ecchymosis.

9 [Slide.]

10 The time to first injection site reaction,
11 the median time was 11 days in the anakinra group
12 and 3 days in the placebo group. Typically, these
13 injection site reactions occurred within the first
14 4 weeks of starting study drug.

15 [Slide.]

16 Even though patients receiving anakinra
17 tested positively in the screening immunoassays,
18 only 10 of the 1,303 patients tested positive in
19 the bioassay. That is an incidence of 0.8 percent.
20 This would represent potentially clinically
21 neutralizing antibodies.

22 I want to point out that this was positive
23 at only one time point in all 10 subjects, and in
24 subsequent samples, this assay was negative.

25 There was no apparent interference with

1 the efficacy or the safety profile.

2 [Slide.]

3 Infections in terms of the incidence in
4 the placebo group, 36.2 percent versus 39.8 percent
5 in the 100 mg anakinra group. Serious infections,
6 this mostly includes patients hospitalized as a
7 result of the infection, 0.7 percent in the
8 placebo, 1.8 percent in the 100 mg anakinra group,
9 and I will be discussing the details in subsequent
10 slides.

11 Interestingly, with regard to withdrawal
12 due to infections, this occurred at a similar
13 incidence across groups of about 1 percent.

14 [Slide.]

15 As I pointed out, the incidence of any
16 serious infections was 0.7 percent in placebo, 1.8
17 percent in the 100 mg anakinra group. The most
18 common serious infection was pneumonia, which
19 occurred in 14 patients in the anakinra group, 0.6
20 percent, versus none in the placebo group. I will
21 be discussing pneumonia also subsequently in more
22 detail.

23 Cellulitis or abscess was reported as the
24 second most common infection. This occurred also
25 at a somewhat higher incidence in the all anakinra

1 group versus placebo, and this mostly represents
2 toe and foot infections, leg infections.

3 In terms of other respiratory infections
4 excluding pneumonia, and this includes nonspecific
5 respiratory infections, upper respiratory
6 infections, bronchitis, the incidence was similar
7 across groups.

8 We noticed that there were three cases of
9 bursitis in patients receiving anakinra. Two of
10 these were olecranon or elbow bursitis, and one was
11 a case of bunion surgery.

12 There were two cases of osteomyelitis in
13 the 100 mg anakinra group. One was a
14 staphylococcal toe infection, and the other one was
15 an epidural abscess, which also involved bone.

16 There was one case of pelvic inflammation
17 and then one case of Herpes Zoster, which was not a
18 complicated case, and resolved quickly.

19 Now, since opportunistic infections have
20 been observed with TNF sequestering agents, it was
21 important for us to look at our database of more
22 than 2,600 patients, and I want to point out that
23 we did not see any cases of mycobacterium
24 tuberculosis, pneumocystis, listeria,
25 histoplasmosis.

1 [Slide.]

2 A by-patient listing of the 14 patients
3 with serious pneumonia is shown on this slide. I
4 just want to make a few points.

5 One is that in the majority of these
6 cases, the causative agent was not identified
7 definitively. In one case, it was identified as
8 streptococcal pneumonia, and in another case,
9 Legionella pneumophila was identified.

10 With regard to the medical history, notice
11 that the majority of these patients, 9 out of 14,
12 had a relevant medical history of COPD, chronic
13 obstructive pulmonary disease, asthma, pneumonia,
14 and other diseases as shown here.

15 With regard to concomitant medications, 11
16 out of the 14 of these patients were receiving
17 concomitant corticosteroid therapy, and the
18 majority of them were also receiving concomitant
19 methotrexate.

20 Note also that in terms of the outcome,
21 the majority of these patients continued in the
22 study.

23 [Slide.]

24 The characteristics of the patients
25 experiencing serious pneumonia are summarized on

1 this slide, and for reference I am also including
2 the characteristics of the all anakinra group from
3 the five placebo-controlled studies.

4 Note that the mean age was approximately
5 61 years, which is slightly higher than what was
6 seen in the all anakinra group. The time to onset
7 was approximately three months. The duration was
8 relatively short, at approximately 12 days.

9 Notice that none of these patients died as
10 a result of pneumonia, and a minority of them were
11 withdrawn from study due to the event.

12 In terms of relevant medical history, most
13 of these patients had, as I pointed out earlier, a
14 relevant medical history, and for asthma, it was
15 about 36 percent versus 8 percent in the all
16 anakinra group. The same was true for chronic
17 obstructive pulmonary disease and a history of
18 pneumonia.

19 With regard to concomitant medications
20 most of these patients were receiving relevant
21 concomitant medications, notably corticosteroids at
22 79 percent versus about 57 percent in the all
23 anakinra group.

24 [Slide.]

25 Now, in order to understand the risk for

1 the serious infections in more detail, we examined
2 a long list of potential risk factors, and a
3 partial list is shown on this slide.

4 I want to emphasize that none of these
5 risk factors examined clearly showed an increased
6 risk associated with infections in patients
7 receiving anakinra, but some of these are of
8 interest and I will show that in subsequent slides.

9 [Slide.]

10 The first is a history of asthma. If we
11 look at the incidence of serious infection in
12 patients with a history of asthma prior to entering
13 into the study, the incidence was 4.5 percent in
14 the anakinra group versus 1.4 percent in the
15 anakinra group in patients who did not have a
16 history of asthma. This same pattern was not
17 observed in the placebo group.

18 With regard to serious pneumonia, a
19 similar trend was seen, 2.8 percent versus 0.5
20 percent. We did not see any cases in the placebo
21 group.

22 [Slide.]

23 We also looked at patients with a history
24 of pneumonia prior to entering into the study, and
25 again, in patients with a history receiving

1 anakinra, it was 2.7 percent versus 1.6 percent in
2 the patients without a history of pneumonia. Again
3 the same pattern was not observed in the placebo
4 group. Pneumonia showed a similar trend.

5 [Slide.]

6 Of interest was concomitant corticosteroid
7 use. The incidence in patients in the anakinra
8 group receiving concomitant corticosteroids was 2.1
9 percent versus 1.1 percent in patients not using
10 concomitant steroids, so that is a ratio of about
11 2.

12 Notice, though, that in the placebo group,
13 there was an incidence of 0.9 percent versus 0.3
14 percent in steroid users versus non-users. This is
15 a ratio of 3.

16 Serious pneumonia, 0.9 percent versus 0.3
17 percent. This indicated to use firstly that we
18 confirmed what is known, and that is, that
19 concomitant corticosteroid use would increase your
20 risk for infection, but then secondly, and more
21 interestingly, is that it appears that anakinra use
22 and steroid use are independent risk factors for
23 serious infection.

24 [Slide.]

25 Results from the previous three tables are

1 summarized graphically in this slide. What I am
2 showing here is the relative risk of having a
3 serious infection for the anakinra group, shown in
4 orange, and the placebo group, shown in white.

5 You can see that in patients with a
6 history of asthma compared to patients without a
7 history of asthma, the point estimate was higher in
8 the anakinra group versus the placebo group.

9 Notice, though, that there is a large confidence
10 interval here, so we cannot conclude definitively
11 that there is an association with this risk factor.

12 With regard to the history of pneumonia,
13 again, there was a higher point estimate in the
14 anakinra group versus placebo, but again, notice
15 the large confidence interval.

16 Interestingly, with regard to concomitant
17 corticosteroid use, the relative risk in both the
18 anakinra and the placebo group was increased, but,
19 if anything, in the placebo group, it was higher
20 versus anakinra. Again, notice the large
21 confidence interval.

22 [Slide.]

23 When we examined the data for the most
24 common infections observed, and this is
25 irrespective of whether it is serious or not, this

1 was upper respiratory infection, sinusitis, and
2 flu-like symptoms, and the incidence was similar
3 across groups.

4 [Slide.]

5 It is known that in patients with
6 rheumatoid arthritis, there are several laboratory
7 abnormalities, for example, anemia, thrombocytosis,
8 and white blood cell and neutrophil abnormalities.

9 What I am showing in this slide is the
10 profile for the mean white blood cell and
11 neutrophil counts over time for the placebo and the
12 100 mg anakinra group. I just want to make a few
13 points here.

14 One is anakinra causes a slight decrease,
15 well within the reference range shown here, of
16 white blood cell count and neutrophil count, which
17 occurred within the first four weeks. Notice,
18 though, that this was not a progressive effect as
19 this level stabilized, and also notice that
20 following anakinra treatment, this level was closer
21 to the midpoint of the reference range compared
22 with the placebo group.

23 [Slide.]

24 Interestingly, anakinra treatment also
25 caused an improvement, although modest, in the

1 hemoglobin, as shown here. Then, with regard to
2 the platelet count, there was a slight decrease,
3 but well within the reference range of the platelet
4 count.

5 [Slide.]

6 Even though we have observed some mild
7 decreases in white cell count and neutrophil count
8 with anakinra, Grade 1 leukopenia of 8.6 percent in
9 anakinra versus 2 percent in the placebo group, in
10 terms of the more severe decreases in white cell
11 count and neutrophil count, we saw very, very low
12 numbers.

13 What I am showing on this slide is the
14 World Health Organization toxicity grade
15 abnormalities observed during treatment, and I am
16 showing this for the white blood cell counts in
17 terms of Grade 2, Grade 3, or Grade 4
18 abnormalities, and the same for the neutrophil
19 decrease.

20 Notice that there were no Grade 4 cases of
21 leukopenia or neutropenia. There was only one case
22 of Grade 3 leukopenia, and this patient is also
23 reflected in the four patients in the neutropenia
24 row.

25 When we look at the neutropenia Grade 3,

1 we notice that there were six cases in total in the
2 anakinra group, who had decreases in neutrophil
3 counts below 1,000. There was only one case out of
4 1,303 patients, an incidence of 0.08 percent at the
5 100 mg recommended dose.

6 None of these patients had any serious or
7 severe infections.

8 [Slide.]

9 Now, the data I showed you on the previous
10 slide represents the five randomized,
11 placebo-controlled trials. We also examined all of
12 the anakinra studies to determine how many cases we
13 have had of patients with a decrease below 1,000 in
14 the neutrophil count, and we identified two more,
15 so there were 8 patients in total, and a by-patient
16 listing of these patients is shown in this and the
17 subsequent slide.

18 I just want to make a few points again.
19 One is that two out of the four patients on this
20 slide had a baseline neutrophil count that was
21 below normal. Notice also that in three of the
22 four patients, the last available neutrophil count
23 was higher than the lowest neutrophil count. Two
24 of these patients were withdrawn from study, and in
25 one of these patients, there was a non-serious

1 tooth and eye infection and oral ulcers.

2 [Slide.]

3 The remaining four patients are shown
4 here. Again note that three out of the four
5 patients had abnormal neutrophil counts at
6 baseline, and the last available neutrophil count
7 in all four of these cases was higher than the
8 lowest neutrophil count. This would suggest that
9 this effect is reversible.

10 I want to point out also that there was
11 one patient in the multi-dose pharmacokinetic study
12 who most likely had Felty syndrome since this
13 patient had evidence of splenomegaly before
14 entering into the study based on a scan conducted,
15 and this patient also had very high rheumatoid
16 factor levels at more than 2,000 International
17 Units per milliliter with the upper limit of normal
18 at 30, and also very high immunoglobulin G, A, and
19 M levels.

20 [Slide.]

21 In addition to looking at the actual
22 laboratory data to identify abnormalities, we also
23 looked at the adverse event data to identify
24 patients who were withdrawn from study due to
25 leukopenia or granulocytopenia.

1 I want to point out that in the earlier
2 protocols, the monotherapy study, the methotrexate
3 combination study, and also the low dose
4 monotherapy study, there was protocol- mandated
5 withdrawal in these protocols, and the levels are
6 specified here.

7 In the two later studies, the large safety
8 study and the confirmatory efficacy study, there
9 were no such protocol-mandated withdrawal criteria.

10 Notice that only 17 of the 2,606 patients,
11 an incidence of 0.7 percent, were withdrawn for
12 this reason. The one patient which I already
13 mentioned possibly had Felty syndrome, 7 of the 17
14 patients, 41.2 percent, received doses greater than
15 100 mg anakinra, and also note that two of these
16 patients never had a neutrophil count which
17 decreased below 2,000.

18 Twenty-four percent of these patients had
19 a level which decreased below 1,000. Again, I want
20 to emphasize none of these patients experienced
21 serious infections, and there were only three cases
22 of infections, two of urinary tract infection, and
23 one of a head cold.

24 [Slide.]

25 We also wanted to see whether there was a

1 possible association between a low neutrophil count
2 and infections, and that data are shown here. You
3 can see that in the 47 patients in the anakinra
4 group who had levels below 1.5 of the neutrophils,
5 none of these patients had serious pneumonia or
6 serious infection.

7 So, in summary, with regard to the white
8 blood cell profile, severe neutropenia, less than
9 500, was seen rarely at 0.04 percent. There was
10 only one subject, and this was the subject with
11 probably Felty.

12 Neutrophil decrease below 1,000 occurred
13 uncommonly, incidence of 0.3 percent, mostly in
14 subjects who were neutropenic before entry into the
15 study. It did not lead to serious or severe
16 infections in these patients. It was transient
17 with a median duration of seven days in patients
18 with available data, and it was reversible in all
19 subjects.

20 [Slide.]

21 Amgen also conducted in response to a
22 request from the FDA an anakinra/etanercept
23 combination study. This was an open-label,
24 single-arm study, in which all patients were
25 receiving etanercept for at least 12 weeks at the

1 standard dose of 25 mg twice a week. The dose of
2 anakinra was 1 mg/kg/day given subcutaneously, 58
3 patients were receiving study drug for a period up
4 to 24 weeks. This study was done in the U.S., and
5 the primary endpoint was serious adverse event.

6 [Slide.]

7 The baseline characteristics are
8 summarized on this slide. The mean age was
9 approximately 49 years, which is somewhat lower
10 than what we have seen in the other anakinra
11 studies. Most of these patients were women as
12 would be expected.

13 Notice that these patients have been on
14 etanercept for a mean period of more than one year.
15 They also had rheumatoid arthritis for an average
16 period of 12 years. So, these were relatively
17 young patients with relatively long-standing
18 rheumatoid arthritis.

19 Also, notice that these patients still had
20 quite significant residual disease despite being on
21 etanercept treatment - a mean tender/painful joint
22 count of 26, swollen joint count of 17, and
23 C-reactive protein of 2.2.

24 [Slide.]

25 With regard to the adverse event profile,

1 there were no deaths seen. There were seven
2 serious adverse events, two of cellulitis, one was
3 a facial cellulitis, and the other one was an
4 abdominal wall cellulitis with abscess, two cases
5 of pneumonia. All four of these patients were
6 hospitalized, managed with intravenous antibiotics,
7 and they all recovered. One case of accidental
8 electrocution, one of opiate, barbiturate
9 withdrawal, and one gastric ulcer hemorrhage in a
10 patient on naproxen.

11 [Slide.]

12 Even though efficacy was not formally
13 analyzed in this study, we did look at changes from
14 baseline in some of the ACR components, and those
15 are shown here for tender/painful joint counts,
16 swollen joint count, Health Assessment
17 Questionnaire, C-reactive protein, and erythrocyte
18 sedimentation rate. You can see that in all of
19 these parameters, there was a mean change decrease
20 from baseline observed.

21 Now, I should point out that this was an
22 open-label study without a control group, so the
23 results should be interpreted in that light.

24 [Slide.]

25 Amgen is also conducting a study in

1 pediatric patients with juvenile rheumatoid
2 arthritis. The study design is shown here. This
3 was a randomized study with two stages. Stage 1 is
4 a 12-week open-label stage, and Stage 2 is a
5 16-week, blinded, placebo-controlled stage.

6 The dose of anakinra is 1 mg/kg/day given
7 subcutaneously up to a maximum dose of 100 mg. The
8 targeted number of patients to be enrolled in Stage
9 1 is 204, and in Stage 2, 68. The total duration
10 of the study is 30 weeks including a two-week
11 follow-up period.

12 The study is being conducted in North and
13 South America, Europe, and Australia. The primary
14 endpoint is disease flare during the blinded
15 period. As of last week, Amgen has enrolled 34
16 patients in the study, and the study is ongoing.

17 [Slide.]

18 The study schema is shown here. After
19 screening and eligibility assessments, patients
20 will be enrolled. They would receive 1 mg/kg/day
21 of anakinra up to a maximum of 100 mg for a 12-week
22 period.

23 At the end of the 12-week period, they
24 would be assessed in terms of the JRA core set
25 criteria for efficacy, and if they responded, they

1 would qualify for the second phase. They would be
2 randomized in a 1 to 1 ratio, anakinra to placebo,
3 and then at the end of the 16-week treatment
4 period, there is a two-week follow-up period.

5 At the end of the study, these patients
6 would qualify for an extension period or an
7 extension study. Nonresponders from the first 12
8 weeks would not qualify for the blinded phase, and
9 these patients would exit the study.

10 [Slide.]

11 So, in summary, Amgen has a large safety
12 database in the treatment of patients with
13 rheumatoid arthritis. More than 2,600 patients
14 have received at least one anakinra dose, and the
15 total patient exposure accumulated is 1,873 patient
16 years.

17 In terms of serious infections, there is a
18 low incidence, 1.7 percent in anakinra versus 0.7
19 percent in the placebo group. The most common
20 serious infection was pneumonia. The risk is
21 possibly higher in patients with a history of
22 asthma.

23 With regard to neutrophil decreases below
24 1,000, this was rare at 0.3 percent. It was
25 reversible and did not appear to be of clinical

1 consequence.

2 So, in conclusion, based on the efficacy
3 profile presented earlier by Moraye Bear, and the
4 safety profile, we believe that Amgen has a very
5 favorable profile in the treatment of patients with
6 this disease.

7 [Slide.]

8 I would like to ask Dr. Stanley Cohen to
9 make some concluding remarks.

10 Concluding Statements

11 Stanley Cohen, M.D.

12 DR. COHEN: Thanks, Dr. Bekker, and good
13 morning. I am Stanley Cohen. I am a
14 rheumatologist for St. Paul Medical Center in
15 Dallas, Texas.

16 I have had the opportunity over the last
17 20 years to be involved in clinical trials and
18 clinical trial design. Over the last decade, I
19 have been the principal investigator on five trials
20 evaluating anakinra in rheumatoid arthritis.

21 Our group has enrolled 60 patients in
22 these trials. Several of these patients, I have
23 had the opportunity to follow for several years.

24 For that reason, Amgen has asked me to
25 provide my perspective on the clinical trial

1 results, as well as to give my thoughts on how we,
2 as rheumatologists, might use this therapy upon
3 approval.

4 [Slide.]

5 It was clear from the clinical trials of
6 the last several years that although things portend
7 to be much better as we move forward, and certainly
8 in the clinic with the newer agents, the new TNF
9 inhibitors, the new DMARDs, such as leflunomide, we
10 have seen better short-term and intermediate
11 outcomes in our patients.

12 Certainly, we have been able to salvage
13 our patients on DMARDs who were partially or
14 nonresponsive with these newer therapies, but it
15 was clear from the clinical trial data that even
16 with the ACR responses seen, that we saw ACR20
17 responses in the range of 40 to 70 percent
18 depending on the clinical data set analyzed, which
19 suggested that 30 to 60 percent of the patients
20 even receiving the newer therapies still had
21 ongoing active disease.

22 Certainly, that type of response has been
23 mirrored in our experience in our clinical
24 practice. We have recently done a chart review,
25 and we looked at the number of patients that we put

1 on infliximab, 131 patients over the last nine
2 months. Of those patients, 20 patients have
3 already discontinued therapy, 15 percent for either
4 lack of efficacy of adverse events.

5 We have seen a similar drop-off rate with
6 the other TNF inhibitor etanercept, so certainly
7 there is still a significant number of patients
8 with moderate to severe disease who require
9 additional therapy.

10 [Slide.]

11 Dr. Bear has shared with you the ACR
12 composite responses, and I wanted to focus on some
13 of the individual components of the ACR response.
14 I chose to show the 180 study as I was the
15 principal investigator on this study, and we have
16 just had this paper accepted for publication in
17 A&R.

18 One of the things that I have been
19 interested in along with several others of my
20 colleagues is patient directed outcomes, and what
21 we have seen is that patient directed outcomes,
22 such as the patient's global rating, patient's pain
23 rating, and HAQ scores or disability and function
24 ratings are less susceptible to the placebo
25 response than are potentially the physician

1 directed outcomes.

2 We presented this data last year at the
3 ACR meeting with the leflunomide data set, and
4 again with this data set, we see a very similar
5 phenomenon where patients on the higher doses of
6 anakinra have a significant response in patient
7 directed ratings that differentiates from the
8 placebo responders more significantly than seen
9 with the physician directed outcomes.

10 [Slide.]

11 The 145 confirmatory study, a similar
12 group of patients partially or nonresponsive to
13 methotrexate, again, similar direction--we haven't
14 done the analysis yet--would suggest that patient
15 directed outcomes, patient's global rating,
16 patient's pain rating, and again, health-related
17 quality of life, physical function disability may
18 differentiate better this active therapy from the
19 placebo response.

20 [Slide.]

21 Lastly, Dr. Bear presented data from the
22 0560 study, which is a very exciting study to us as
23 clinical rheumatologists, as this was the first
24 study of only six months' duration to suggest that
25 there might be blunting of x-ray progression.

1 This is the modified Sharp total score,
2 the scoring system that we, as U.S.
3 rheumatologists, are more comfortable with and
4 accustomed to using, and again, the data here shows
5 that in the placebo group, over six months, a
6 worsening of modified Sharp score, 3 1/2 units, and
7 then all the anakinra-treated patients, there was a
8 blunting of this x-ray progression by close to 40
9 percent.

10 We await the 12-month analysis of the 145
11 data to determine if this suggestion of x-ray
12 improvement will be carried over into the 12-month
13 outcome.

14 [Slide.]

15 Turning to the risk of anakinra or my
16 perspective on the risk, injection site reactions
17 certainly occur with anakinra, and we, as
18 rheumatologists, are very comfortable with
19 injection site reactions with injectable TNF
20 products that we are now using.

21 We have become more experienced in
22 managing injection site reactions. We have learned
23 to properly educate our patients, to let them know
24 that the majority of these are transient,
25 short-lived, that these can be managed, if

1 necessary, with topical antihistamines or
2 corticosteroids, and in this data set, as you saw,
3 only 7 percent of patients in the clinical trials
4 had to discontinue anakinra due to injection site
5 reactions, and I suspect that this number will be
6 even less in the real world experience because we,
7 as rheumatologists, are more comfortable with
8 managing injection site reactions.

9 The overall infection rate was similar
10 between the placebo group and the group receiving
11 anakinra, but there was a slight increased risk in
12 serious infection albeit it at a rate lower than or
13 similar to what has previously been published in
14 data sets on the TNF inhibitors.

15 There was a rare decrease in the overall
16 white blood cell count and neutrophils, and I will
17 have a few more comments about that as I conclude
18 with my remarks about how I am considering
19 monitoring these patients.

20 One of the concerns would be with this
21 therapeutic that is the daily injectable and will
22 patients continue to inject themselves on a daily
23 basis. I think the clinical trial results support
24 that indeed the answer is yes, they will, as long
25 as they are seeing clinical benefit. Compliance in

1 the trials was excellent throughout all the
2 particular trials performed.

3 The flip side of this, however, is that
4 the daily injectable may be an advantage to this
5 particular biologic in that it has a short
6 half-life, and in case of an adverse event, such as
7 an infection, by discontinuing anakinra, within 24
8 hours, the plasma levels return to near baseline,
9 and therefore, the patient's ability to deal with
10 an infection might be enhanced by removal of the
11 biologic, which is a problem that we have with some
12 of the other biologics we are presently using that
13 have longer half-lives.

14 [Slide.]

15 So, what are my thoughts on practical
16 guidance for looking after patients on anakinra? I
17 think the most important for all us, as
18 rheumatologists, with all the therapeutics, is
19 proper patient selection.

20 These therapeutics are for patients with
21 moderate to severe rheumatoid arthritis. I think
22 it is important that we select the patients who are
23 most likely to have a poor, long-term outcome with
24 their rheumatoid arthritis. These are the patients
25 we want to treat with these agents including

1 anakinra.

2 Certainly, we have learned. The
3 experience over the last several years is that we
4 want to avoid patients who have an acute infection,
5 and we want to avoid patients who have chronic
6 infection, do not increase the risk of problems
7 with these agents.

8 Patient education is paramount. I think
9 that it is clear, as I have said earlier, that with
10 proper patient education, I think that very few
11 patients will have to discontinue anakinra due to
12 injection site reactions, again, just another level
13 of experience that we have learned as clinicians.

14 Infection precautions are also very
15 important. We, in our clinic, instruct all of our
16 patients on biologics, and anakinra would be no
17 different, that if you have any signs or symptoms
18 suggestive of infection, that we want to hear from
19 you immediately, not two to three days later, we
20 want to hear from you immediately, so we can assess
21 the situation and decide whether we need to
22 intervene with antibiotic therapy.

23 Based on the data that Dr. Bekker showed
24 you, I feel that patients who have a low baseline
25 neutrophil count upon initiation of anakinra,

1 should be monitored with serial CBCs, however, as I
2 feel that most of these patients will be on
3 combination therapy with DMARDs, we are presently
4 monitoring DMARDs in that fashion.

5 [Slide.]

6 So, which patients do I think should get
7 anakinra? Well, based on the data sets presenting
8 this morning, I think that patients who fail DMARDs
9 could potentially be candidates for anakinra.

10 The 0560 data from Europe suggest that
11 anakinra could be used as a monotherapy, however, I
12 think that the large majority of patients are going
13 to be those patients who lack a full response to
14 disease-modifying agent, and most patients in this
15 country are on methotrexate as their baseline
16 disease-modifying agent.

17 However, we do know from the 757 safety
18 study that anakinra can be used safely in
19 combination with multiple other DMARDs, such as
20 leflunomide and sulfasalazine and plaquenil. So, I
21 think the large majority of patients will be using
22 this in combination therapy.

23 I think there will be a role for patients
24 who are presently on biologic agents, who are
25 intolerant to these agents, or nonresponsive to the

1 agents, that we will be able to switch to this new
2 protein in hopes of decreasing inflammation through
3 a different pathway.

4 I think we need more data before we
5 consider the use of combination biologic agents,
6 and we look forward to that data in the near
7 future.

8 [Slide.]

9 So, in summary, anakinra, as you have seen
10 this morning, has unique mechanism of action. It
11 is the first IL-1 inhibitor for rheumatoid
12 arthritis. It is a naturally occurring
13 anti-inflammatory protein.

14 I think it has a favorable risk-benefit
15 profile. You have seen the ACR benefit, the fact
16 that it occurs early, 27 to 31 percent of patients
17 in the trials had a sustained benefit. To me, one
18 of my interests is patient-reported outcomes. It
19 had a very important effect on patient-reported
20 outcomes, health related quality of life and
21 disability.

22 There is suggested evidence that it blunts
23 x-ray progression, and again we remain excited
24 about the data that should be forthcoming in the
25 near future, and the short half-life does allow for

1 rapid clearance of this therapeutic upon
2 discontinuation of therapy, which may enhance our
3 ability to deal with adverse events.

4 So, thank you very much. Dr. Perlmutter.

5 Roger Perlmutter, M.D., Ph.D.

6 DR. PERLMUTTER: Thank you, Dr. Cohen.

7 [Slide.]

8 This completes the presentation from Amgen
9 on anakinra. I would like to just close by
10 reiterating what we seek in terms of anakinra
11 licensing.

12 [Slide.]

13 Our proposed indication for anakinra is
14 that anakinra is indicated for the reduction in
15 signs and symptoms of active rheumatoid arthritis,
16 in patients 18 years of age or older who have
17 failed one or more disease-modifying anti-rheumatic
18 drugs. It can be used alone or in combination with
19 other DMARDs.

20 I believe that the data that we have
21 presented demonstrate that anakinra is effective
22 and can be used safely for this indication.

23 We thank you for your attention. I yield
24 the floor to you, Dr. Harris.

25 DR. HARRIS: Thank you very much, Dr.

1 Perlmutter.

2 I am going to just hold for a few more
3 minutes for any questions that are clarification.
4 Let's start with Dr. Elashoff.

5 DR. ELASHOFF: Yes. This is about Study
6 960180. It sounded like that study was amended
7 after it had begun and that the dose of 1 mg/kg was
8 perhaps not started, enrollment for that was
9 perhaps not started at the time of that enrollment
10 for placebo group was started.

11 Is that correct?

12 DR. PERLMUTTER: I will ask Dr. Bear to
13 address the technicalities of the study.

14 MS. BEAR: The two new doses, the
15 enrollment was concurrent with placebo, so in other
16 words, for the original doses, we were enrolling
17 across the four original doses including placebo,
18 and when we added the two new doses, we also
19 increased the sample size, so we continue to enroll
20 and randomize across all six treatment groups.

21 DR. ELASHOFF: So the randomization ratio
22 was presumably changed in order to get the 1 mg/kg
23 up to speed while not enrolling that many more
24 placebo?

25 MS. BEAR: That's correct. After the

1 amendment, the randomization ratio was changed, so
2 that at the end, at week 12, we had approximately
3 70 patients across all of the six treatment groups
4 including the two new doses.

5 DR. ELASHOFF: How long after enrollment
6 began for the placebo group was this other group
7 added?

8 MS. BEAR: Well, I think there were about
9 105 patients already enrolled under the old
10 amendment.

11 DR. BRANDT: I have two questions, and
12 they are both radiologic in a sense. Was there any
13 correlation attempted to look at the relationship,
14 if it existed, between clinical improvements and
15 radiographic improvement in individual subjects?
16 You presented mean data.

17 DR. PERLMUTTER: Again, Moraye Bear will
18 address that.

19 MS. BEAR: Yes, there was. If we could
20 bring up Slide R-814.

21 [Slide.]

22 In Study 0560, what this shows is the
23 patients who were ACR20 responders and the patients
24 who were nonresponders at week 24. We see here the
25 median change from baseline for the Larsen score

1 among both of these subgroups. In general, we can
2 see that the patterns were generally similar, we
3 see decreasing Larsen scores for each of the
4 treatment groups.

5 So, in general, the relationship between
6 change from Larsen scores did not seem to be
7 mediated by whether or not you were an ACR20
8 responder or not.

9 DR. BRANDT: The other question relates to
10 the radiographic analysis, because IL-1 not only
11 inhibits cartilage matrix metalloproteinase
12 production, but also proteoglycan synthesis.

13 In the radiographic analyses, was there
14 any attempt to look at people who actually enlarged
15 their joint space, because you presented
16 differences in mean rate of narrowing. Within,
17 there are some patients with widened joint space.

18 DR. PERLMUTTER: Right. So, there was, of
19 course, scoring of the joint space in general
20 terms, and Moraye may want to address this or
21 perhaps Dr. Genant could speak to this issue if he
22 is available.

23 DR. GENANT: It is a very interesting
24 point, Dr. Brandt. Since in the interpretation of
25 the radiographs, I was blinded to treatment, I did

1 not have an awareness of an increase in joint
2 width. We have not, to my knowledge, undertaken an
3 analysis looking specifically at that issue.

4 DR. WILLIAMS: I had one question about
5 the joint swelling. It appeared that in many of
6 the studies, there was little change in the median
7 joint swelling, yet you had significant changes in
8 the ACR20.

9 Does that mean that there were significant
10 numbers of patients who had worsening of joint
11 swelling?

12 DR. PERLMUTTER: Moraye Bear again will
13 answer that.

14 MS. BEAR: No. In fact, in 0560, there
15 were significant differences among the swollen
16 joint counts. In 145, I could put the slide back
17 up if you would like me to, we didn't see
18 significant differences at week 24, but clearly, we
19 saw that anakinra-treated patients throughout the
20 treatment period were benefitting relative to
21 placebo patients in the swollen joint counts.

22 DR. FELSON: Actually, a similar question
23 to Jim's. I think Stan Cohen commented on the
24 patient-specific outcomes, and it is interesting,
25 looking at the sort of spectrum of outcomes here,

1 that it looks like those outcomes and especially
2 acute phase reactants respond, and swollen joint
3 counts seem to respond much less to this agent.

4 I guess one wonders whether if you used a
5 composite efficacy measure without acute phase
6 reactants, whether you would get a significant
7 result. There are such composite measures. They
8 include the preliminary ACR before we added acute
9 phase reactants, and they actually include the
10 EULAR index, which uses DAS, which the DAS includes
11 the sed rate, but it doesn't weight it very much.
12 It is mostly a swollen and tender joint count.

13 I am wondering if you have the EULAR
14 definition of response and whether, in your pivotal
15 trial, 145, I think it is, a large pivotal trial,
16 whether you measured EULAR response rates and
17 whether they were different in the two groups.

18 DR. PERLMUTTER: Of course, the studies
19 were designed based on ACRs, and we could have a
20 long discussion, I think, which you are well
21 informed about, and which Dr. Cohen alluded to,
22 about the relative value of each one of the
23 components of the ACR score, but, Moraye, again,
24 perhaps you would like to just briefly speak about
25 this issue.

1 MS. BEAR: In 145, we have not done that
2 analysis. I believe we have done that analysis in
3 previous studies and shown that there was benefit
4 for anakinra, but I don't have that data to show
5 you today.

6 DR. HARRIS: I am going to have Dr.
7 Elashoff first and then Dr. Williams, then, we will
8 go to Dr. Katona.

9 DR. ELASHOFF: This question is for Moraye
10 Bear. It has to do with Table 4-9 on page 61 of
11 the briefing document, which shows the percent of
12 responders at week 24 depending on whether they
13 have injection site reaction or not, there are p
14 values comparing placebo to anakinra for subjects
15 without and subjects with ISR, but what I would
16 like to know is what is the p value in the placebo
17 group comparing percent responders, which is 19
18 percent in the group without ISR, to 31 percent in
19 the group with ISR, what is the p value for that
20 comparison?

21 MS. BEAR: We have not done that analysis.

22 DR. ELASHOFF: I would do it myself, but I
23 don't have a calculator.

24 MS. BEAR: Perhaps we can get somebody
25 here to do that for you.

1 DR. ELASHOFF: Thank you.

2 DR. HARRIS: Perhaps we could do it during
3 the break.

4 Dr. Katona.

5 DR. KATONA: My question is for Dr.
6 Bekker, and it relates to Table 4-19 in the
7 briefing document. There have been apparently some
8 deaths during or after anakinra therapy that wasn't
9 discussed this morning, and just would like to get
10 a little bit of further explanation in addition to
11 what is in our briefing book.

12 DR. BEKKER: Yes, could I have slide
13 ASA-4, please.

14 [Slide.]

15 Yes, you are correct in making that
16 statement. Of course, when we include data from
17 all of the RA studies, there were other deaths, as
18 well, and a total summary is shown in this slide.
19 This includes all of the deaths that we are aware
20 of, so it includes the 19 deaths that I mentioned
21 earlier, and then also 10 additional deaths that we
22 have observed in ongoing studies since the time of
23 the submission, so a breakdown by cause is given
24 here for the anakinra group, placebo, and the
25 blinded group.

1 Cardiovascular disease was the most
2 common. Two of these nine cases were due to
3 cerebrovascular accident. There were five cases of
4 cancer, two gastric, one pancreatic, one melanoma,
5 the non-Hodgkin's lymphoma, and then also one case
6 of small-cell lung cancer.

7 With regard to infections, we observed one
8 case of respiratory infection and failure, one case
9 of pneumonia and sepsis, another case of abdominal
10 wall abscess, and then the last case was a case of
11 again abdominal wall infection.

12 The other causes are shown here. That is
13 what we have in total.

14 DR. HARRIS: Dr. Abramson.

15 DR. ABRAMSON: I just have a couple
16 questions related to the PK data and the dosing.
17 First, I was curious, during the PK studies, did
18 you look at access into the synovial fluid?

19 DR. PERLMUTTER: I am sorry?

20 DR. ABRAMSON: Do you have any data during
21 the PK studies or any of the other studies in terms
22 of detection of anakinra in the synovial fluid and
23 the dose dependence of that?

24 DR. PERLMUTTER: The PK studies, of
25 course, were done for different methods of

1 administration in both normal and in rheumatoid
2 arthritic patients, but there are no comprehensive
3 studies of synovial fluid that permit us to
4 establish what the dose relationship is in exposure
5 for anakinra.

6 DR. ABRAMSON: In terms of choosing the
7 dose, whether there could be dose step-up with the
8 medication, the PK shows that 1 mg/kg is not as
9 good as 2 mg/kg. Your 2 mg/kg data, your high dose
10 tends to outperform in at least several studies,
11 and meet ACR benchmarks to a greater degree.

12 DR. PERLMUTTER: Yes.

13 DR. ABRAMSON: In another setting, 75 kg
14 was the mean weight of the patient population. The
15 question is are you at the proper therapeutic dose,
16 is there any thought of a stepping-up of the dose,
17 or how do you view that issue, are you underdosing
18 based on your own PK data and your clinical
19 outcomes?

20 DR. PERLMUTTER: It is a very fair
21 question. We wrestled with this question, as you
22 can imagine, quite a bit. In examining all of the
23 data that we had and, of course, that you have
24 seen, our feeling was that the best therapeutic
25 index, the best balance in terms of efficacy versus

1 potential adverse effects was achieved at the 100
2 mg dose. That is the one we decided to go forward
3 with also based on, of course, the way in which it
4 would be administered, being able to provide a
5 fixed dose syringe, et cetera.

6 It is possible that there could be some
7 additional efficacy in some individuals that could
8 be gained by pushing the dose higher, but from our
9 perspective, the best balance in terms of therapy
10 was at the 100 mg dose, good efficacy, and we
11 didn't want to raise perhaps additional safety
12 concerns. It is a fair point, though.

13 DR. ABRAMSON: Have you analyzed whether
14 CRP or sed rate, both of which do nicely with the
15 drug, predict responders in any way, early changes
16 in those markers?

17 DR. PERLMUTTER: We have tried to look at
18 that directly, and, Moraye, perhaps you would want
19 to speak to that issue.

20 MS. BEAR: In general, reductions in the
21 acute phase reactants tend to be similar across all
22 dose groups, so there is no overall predictiveness
23 there. I mean anakinra will reduce them.

24 DR. ABRAMSON: And people who respond have
25 comparable early--

1 MS. BEAR: In general, yes.

2 DR. PERLMUTTER: I think, Steve, you have
3 seen that kind of thing before in other treatment
4 protocols.

5 DR. HARRIS: Can I ask, the cases of
6 cellulitis and abscess, did they occur at the
7 injection site?

8 DR. BEKKER: That was an interesting
9 finding, that when I examined the data, none of the
10 cases of serious cellulitis was actually at the
11 injection site, so most of these were lower
12 extremity, toe and foot infections, leg infection,
13 and in a patient with cat scratch, and so on, and
14 in terms of injection site infections, we have
15 really seen very, very few of those cases. I can
16 recall one that we have seen. The patient
17 recovered and continued in the study.

18 DR. HARRIS: And a follow-up question. In
19 patients where the neutropenia may have been severe
20 enough to withdraw therapy, did you re-challenge
21 any of them again to see what happened?

22 DR. BEKKER: We do not have any data on
23 that, no.

24 DR. HARRIS: Okay. Well, it seems that we
25 have exhausted our questions, and we are going to

1 have a break of 15 minutes. Thank you.

2 [Recess.]

3 DR. HARRIS: We will resume the session,
4 the second part of our morning session. I will ask
5 while it is fresh in our mind, that Dr. Bear wanted
6 to respond to the question raised by Dr. Elashoff.

7 MS. BEAR: Yes. In response to Dr.
8 Elashoff's question on Table 4-9 in the briefing
9 document, the comparison between the two placebo
10 groups is 0.0755 by likelihood ratio test and
11 0.0680 by Pearson chi square.

12 DR. HARRIS: Okay. Thank you.

13 Now, we are going to proceed with the
14 presentation from the FDA. Dr. Raymond Donnelly.

15 FDA, CBER Presentation
16 Overview and Introduction
17 Raymond P. Donnelly, Ph.D.

18 DR. DONNELLY: Good morning.

19 I would like to introduce the second phase
20 of our discussion this morning, and that is a
21 discussion of Kineret (anakinra) from the FDA
22 perspective, which may differ somewhat from the
23 Amgen perspective.

24 [Slide.]

25 Let me introduce the review team at CBER

1 that was responsible for the initial review of this
2 application. It is very much a team approach and
3 includes many individuals, not all of whom are
4 listed here, but this is the primary review team,
5 which includes myself, as the product reviewer,
6 that is, the individual responsible for the review
7 of the chemistry, manufacturing, and control
8 information; Jeffrey Siegel, who will be speaking
9 shortly, with regards to the clinical data.

10 Jeffrey Siegel is the primary reviewer for the
11 clinical information.

12 He was assisted in part by George Mills
13 specifically with regards to the radiographic
14 imaging data. Deborah Bower was the bioresearch
15 monitor assigned to this application. Boguang Zhen
16 was our biostatistician. Anne Pilaro reviewed the
17 preclinical pharmacology and toxicology data.
18 Laurie Paserchia and subsequently Dave Greene,
19 whose name is not listed here, reviewed the
20 clinical pharmacology components. Reggie Neal in
21 Compliance, and perhaps most importantly, Vicky
22 Tyson, who is the regulatory project manager, who
23 made sure that we met the deadlines for review.

24 [Slide.]

25 This application was initially received at

1 the Agency on December 28th, 1999, just prior to
2 the advent of the new Millennium. It was assigned,
3 after initial filing assessment, it was assigned a
4 standard 10-month review. In April 2000 and at
5 Amgen's request, we performed a prelicense
6 inspection somewhat ahead of schedule, and that
7 inspection was headed by Reggie Neal from the
8 Division of Manufacturing and Product Quality
9 Control, and he was assisted by John Finkbohner
10 also from that division, myself, and from the
11 Denver District Office, Grace McNally.

12 On November 17th of last year, CBER issued
13 a complete review letter, which was sent to Amgen,
14 which cited specific issues that the sponsor needed
15 to address in order for this application to move
16 forward towards potential approval. These included
17 issues with regards to the clinical information,
18 preclinical data, and product-related issues.

19 Approximately, 3 1/2 months later, we
20 received a formal response from Amgen, and that
21 response was classified as a Class 2 resubmission,
22 meaning that it has a six-month review time.

23 [Slide.]

24 Just to reiterate what Dr. Perlmutter
25 discussed earlier this morning, Kineret or anakinra

1 is a recombinant form of human IL-1 receptor
2 antagonist. This protein is expressed in E. coli.
3 The amino acid sequence of the purified protein is
4 identical to that of native human IL-1ra except for
5 the addition of an N-terminal methionine to
6 facilitate expression in E. coli.

7 The molecular weight of the purified
8 protein is 17.3 kilodaltons.

9 [Slide.]

10 Anakinra is purified through a series of
11 chromatography steps to yield a purified bulk drug
12 substance, which is then analyzed using a
13 predescribed set of physical/chemical methods to
14 evaluate its identity, purity, and potency.

15 The purified bulk drug substance is then
16 formulated and sterile filtered, and the finished
17 drug product is supplied in prefilled syringes as a
18 sterile, clear, colorless preservative-free liquid.

19 [Slide.]

20 Also, as mentioned previously, anakinra
21 inhibits the action of IL-1 by competitively
22 blocking the binding of IL-1 to IL-1 receptors on
23 IL-1-responsive target cells. Pharmacokinetic
24 studies showed that the terminal half-life of
25 anakinra following subcutaneous administration

1 ranges from three to six hours, and there was no
2 evidence of drug accumulation in RA patients after
3 daily dosing for up to 24 weeks.

4 So, with that background in mind, I would
5 like to introduce Dr. Jeffrey Siegel from the
6 Division of Clinical Trial Design and Analysis, who
7 will discuss the safety and efficacy data.

8 Efficacy and Safety

9 Jeffrey N. Siegel, M.D.

10 DR. JEFFREY SIEGEL: Good morning.

11 [Slide.]

12 I will be discussing the safety and
13 efficacy studies that have been done to
14 characterize treatment of patients with rheumatoid
15 arthritis with Kineret.

16 [Slide.]

17 The sponsor's proposed indication for
18 anakinra is as follows: Kineret is indicated for
19 the reduction in signs and symptoms of moderately
20 to severely active rheumatoid arthritis in patients
21 18 years of age or older who have failed one or
22 more disease-modifying anti-rheumatic drugs.
23 Kineret can be used alone or in combination with
24 other disease-modifying anti-rheumatic drugs.

25 [Slide.]

1 I am going to begin by discussing briefly
2 the history of this submission because it is
3 relevant to some of the data that I will be
4 discussing.

5 The Agency initially accepted BLA filing
6 in December of 1999, that contained the results of
7 two randomized efficacy trials of anakinra in
8 rheumatoid arthritis.

9 At the time of that BLA filing, the Agency
10 recommended that Amgen begin additional studies to
11 address certain issues that were not covered by the
12 existing data.

13 [Slide.]

14 Amgen began several additional clinical
15 trials in the year 2000. They began a one-year
16 trial of radiographic progression. They began a
17 six-month randomized safety study with a long-term
18 open-label extension. They began a study of
19 children with juvenile rheumatoid arthritis, and
20 they began a study of anakinra given in combination
21 with TNF antagonists, specifically Enbrel.

22 [Slide.]

23 Upon review of the originally submitted
24 data, the Agency informed Amgen that while the data
25 were suggestive of biologic activity, additional

1 safety and efficacy data would be needed. Amgen
2 responded to the Agency request with data from
3 three additional trials.

4 [Slide.]

5 The trials that I will be discussing are
6 shown here. The new trials whose results were
7 added to the submission are shown in yellow here,
8 and the three studies that were available
9 previously are shown in white. I will go into the
10 details of each of these studies individually.

11 I just want to mention that study 960182,
12 that you have heard a bit about earlier, was a
13 small pilot study of lower doses of anakinra. It
14 did not show efficacy, and I am not going to be
15 discussing this further.

16 [Slide.]

17 I will begin by discussing study 990145.
18 This study had a primary radiographic endpoint at
19 one year and a primary clinical endpoint, which is
20 the one that we will be discussing, at six months.

21 The results that I will be presenting are
22 the results of an interim analysis of all 506
23 subjects who were randomized as of a specific date,
24 namely, May 18, 2000. The study remains ongoing.
25 A total of approximately 900 patients have been

1 enrolled, and the study is closed for
2 randomization, but the study remains blinded.

3 [Slide.]

4 Study 145 enrolled patients with active
5 rheumatoid arthritis with at least one bony erosion
6 on x-rays, who were on stable doses of
7 methotrexate. There was a 1 to 1 randomization to
8 either anakinra 100 mg subcutaneously daily, or to
9 placebo.

10 Because of concerns about bias due to
11 unblinding effects of injection site reactions,
12 independent blinded joint assessors were used for
13 the joint assessment components of the ACR20.

14 The primary clinical endpoint for this
15 study was the ACR20 at six months. In addition,
16 stable doses of NSAIDs and low doses of
17 corticosteroids were allowed.

18 [Slide.]

19 An equal number of patients were
20 randomized into each arm, approximately 250 of
21 these patients, approximately three-quarters, a
22 similar number in each arm completed six months of
23 therapy, and the reasons for not completing six
24 months of therapy are shown at the bottom of table.

25 I will just point out that the withdrawals

1 for adverse events were somewhat higher in the
2 anakinra arm compared to the placebo arm.
3 Withdrawal due to subject request, which was
4 generally lack of efficacy or specifically to RA
5 progression was higher in the placebo arm than the
6 anakinra arm.

7 The mean age of the patients was
8 approximately 56 years, and the baseline
9 demographics were well balanced between study arms.

10 [Slide.]

11 Baseline disease activity is shown here.
12 Approximately three-quarters of the patients were
13 positive for rheumatoid factor, NSAID use and
14 corticosteroid use were present in a majority of
15 patients, and were well balanced between the study
16 arms. The mean methotrexate dose was approximately
17 15, and the duration of RA was about 10 to 11 years
18 in both arms.

19 [Slide.]

20 Patients had highly active rheumatoid
21 arthritis at the time of enrollment. As shown
22 here, approximately 25 tender joints, 20 swollen
23 joints, and a great deal of disease activity based
24 on physician global and patient global, and
25 elevated acute phase reactants. Again, there were

1 no imbalances between study arms noted.

2 [Slide.]

3 The primary endpoint of the study, as I
4 mentioned before, was the ACR20 at six months, and
5 the study showed a statistically significant
6 increase in the proportion of patients who achieved
7 an ACR20 at six months, as shown here, 38 percent
8 compared to 22 percent.

9 A higher proportion of patients achieved
10 an ACR50 and ACR70 response, however, the
11 proportion of patients who achieved these higher
12 levels of benefit were smaller.

13 We analyzed the patients who achieved an
14 ACR20 in the group who did not have injection site
15 reactions, because this is the group that would be
16 less prone to unblinding bias, and similar high
17 responses were seen in the anakinra group, in the
18 subset without injection site reactions.

19 [Slide.]

20 The time course of achieving an ACR20
21 response is shown here. As you can see, a higher
22 response rate was seen by week 4 in the anakinra
23 group, and an increase in the proportion of
24 patients who had an ACR20 continued to increase out
25 to week 20.

1 [Slide.]

2 An improvement was seen in each of the
3 components of the ACR20 with the exception of the
4 swollen joint counts, as were pointed out earlier.
5 We analyzed the time course of the swollen joint
6 counts and at earlier time points, there was a
7 larger decrease in swollen joint counts in the
8 anakinra-treated patients compared to placebo, but
9 by the six-month time point, these two curves had
10 come close to each other.

11 [Slide.]

12 The Agency performed subset analyses and
13 found a similar clinical response on all of the
14 subsets shown here. Similar responses were seen in
15 male and female patients. Similar responses were
16 seen in patients subsetted by ethnicity, in
17 patients who had long duration versus short
18 duration of disease, and patients with highly
19 active disease as measured by the tender joint
20 count.

21 [Slide.]

22 I will show you a few of the other subsets
23 here. When subsetted by age, the difference
24 between anakinra and placebo was less for the upper
25 quartile of patients subsetted by age than it was

1 in the younger patients, however, when this subset
2 was looked at in the other studies, there was no
3 difference between the older and younger patients.
4 So, it is possible that this is due to looking at
5 many different comparisons as we did, but I did
6 want to show you the results anyway.

7 [Slide.]

8 When the patients were subsetted based on
9 rheumatoid factor positivity, similar responses
10 were seen in the positive and negative patients,
11 and when subsetted by an elevated sed rate, as
12 shown here, similar responses were seen in the
13 patients with elevated sed rate and those who had
14 less elevated sed rate.

15 [Slide.]

16 I will go on with the other data of
17 efficacy that we have available. This would
18 include studies 0560 and 960180. These were Phase
19 II and Phase II/III respectively, randomized,
20 double-blind, placebo-controlled trials of
21 anakinra.

22 Both studies enrolled patients with active
23 rheumatoid arthritis by ACR criteria, patients on
24 stable doses of NSAIDs and prednisone, and each
25 included six months of blinded therapy.

1 Study 0560 also assessed radiographic
2 progression, as you have already heard.

3 [Slide.]

4 This table compares some of the
5 differences between the two studies. Other DMARDs
6 were not allowed in study 0560, but background
7 methotrexate was used in all patients in study 180.

8 The primary endpoint of study 0560 was the
9 six-month ACR20. For study 180, the primary
10 endpoint was the three-month ACR20, but the
11 six-month ACR20 was included as an important
12 secondary endpoint.

13 The doses studied were different in the
14 two studies. Fixed doses were used in study 0560,
15 as shown here, 30, 75, and 150, and weight-adjusted
16 doses were used in study 180, varying between 0.4
17 and 2 mg/kg subcutaneous daily.

18 Study 0560 was performed in Europe, and
19 study 180 was carried out in the U.S., Canada, and
20 Australia.

21 [Slide.]

22 I will discuss the results of study 0560
23 first. The patient population enrolled into this
24 study had similar baseline characteristics to the
25 study I presented earlier, study 145, with respect

1 to age, gender, corticosteroid use, rheumatoid
2 factor positivity, and baseline sed rate.

3 Some of the differences that were noted in
4 study 0560 was that the vast majority of these
5 patients were Caucasian, presumably due to the
6 place where the study was carried out, and also a
7 shorter duration of rheumatoid arthritis in this
8 study compared to the earlier study, a mean
9 duration of rheumatoid arthritis of 4 years
10 compared to 11 years in the earlier study.

11 The tender joint counts were 35 in study
12 0560 and 27 in the earlier study.

13 [Slide.]

14 Clinical responses in study 0560 are shown
15 here. The primary endpoint was the week 24
16 responses. You can see that a higher response was
17 seen in each of the three study arms - 40 percent,
18 34 percent, and 43 percent compared to 27 percent
19 in the placebo.

20 The individual nominal p values were 0.5
21 or below for the lowest dose and the highest dose,
22 but the p value was not below 0.05 for the middle
23 dose, so the data do show some inconsistency in the
24 lower dose. The middle dose is not significant
25 while the higher dose is.

1 The p values shown are nominal values
2 because the analytic plan for the study did not
3 describe a plan for adjusting for multiple
4 outcomes. Looking at the individual components of
5 this study showed improvements in all the
6 components of the ACR composite score.

7 [Slide.]

8 The other efficacy study was study 960180.
9 This had similar baseline characteristics to study
10 145 with respect to age, gender, rheumatoid factor
11 positivity, baseline disease activity, and sed
12 rate.

13 Some of the differences noted are shown
14 here. There was a somewhat higher corticosteroid
15 use of 64 percent versus 53 percent, and a somewhat
16 shorter duration of rheumatoid arthritis, 7 years
17 versus 11 years.

18 [Slide.]

19 Clinical responses are shown here. Higher
20 point estimates for the response rate at week 24,
21 higher response rates were seen for the three
22 higher doses. That is all I am showing here in
23 this slide, and the primary analysis was a test for
24 dose response using the Agresti Coull method, and
25 the p value for the overall comparison for dose

1 response was 0.004. The three-month data were also
2 statistically significant, and improvements were
3 seen in all of the components of the ACR criteria.

4 [Slide.]

5 The rheumatoid arthritis guidance document
6 recommends collection of clinical response data
7 throughout the study, and not just at the beginning
8 and the end of the study.

9 To address the issue of responses during
10 the course of the study, the protocol included an
11 assessment of a sustained response, and that was
12 defined as a patient who had an ACR20 response at
13 four of the six monthly measurements, and one of
14 those had to include either the three-month time
15 point or the six-month time point.

16 I would like to make a couple points from
17 this. The placebo response using this sustained
18 responder definition is lower than was seen with
19 the ACR20 at three or six months.

20 In addition, we did not see a dose
21 response in the study 0560, but in this study,
22 which explored lower doses, a clear dose response
23 is seen, with the 0.04 mg/kg dose showing no
24 difference from placebo, and the higher doses
25 showing a clear dose response, although one could

1 argue about whether you seem to be achieving
2 plateau at the higher doses.

3 [Slide.]

4 So, in summary, for the signs and symptoms
5 data that we have available for anakinra, three
6 randomized trials showed a higher proportion of
7 ACR20 responses in anakinra-treated patients
8 compared to placebo. These responses were seen
9 within weeks and were maintained out to six months.

10 Effects were seen on all components of the
11 ACR criteria although the effect on certain
12 criteria were greater than on other criteria, as I
13 have tried to point out. Consistent effects were
14 seen across various subsets based on baseline
15 demographics and baseline disease states.

16 [Slide.]

17 I am going to discuss briefly the
18 radiographic data that we have available, but
19 before I do, I just want to mention that the
20 rheumatoid arthritis guidance document sets forth
21 the criteria that the FDA uses to assess whether an
22 agent has shown improvement for the inhibition of
23 progression of structural damage.

24 The RA guidance document was put together
25 in consultation with this committee, as I am sure

1 you are all aware. The document states that a
2 claim of inhibition of structural damage may be
3 based on the following: the agent should already
4 have demonstrated efficacy for signs and symptoms,
5 and a one-year study should be available showing a
6 decrease in structural damage based on a validated
7 index, such as the Sharp score or the Larsen score.

8 [Slide.]

9 In study 0560, radiographic assessments
10 were obtained at baseline and at six months, x-rays
11 of the hands and wrists, but not the feet. The
12 analyses that were performed on this radiographic
13 data are shown here. The prespecified radiographic
14 endpoint was the Larsen score, and the Sharp score
15 was measured afterwards in a post-hoc re-analysis
16 of the data.

17 I want to point out that baseline and
18 follow-up x-rays are only available for
19 approximately three-quarters of the subjects or 347
20 out of the 472 patients enrolled, so we don't have
21 any information on the radiographic progression in
22 one-quarter of the patients.

23 [Slide.]

24 The prespecified endpoint, as I mentioned,
25 was the Larsen scores, as shown here. Again, as I

1 mentioned, approximately a quarter of the films are
2 unavailable for analysis. The mean baseline and
3 median scores are shown in the middle of the table
4 here, and I want to point out that there were some
5 imbalances between study arms in that the median
6 score at baseline was similar in placebo and the
7 two lower dose anakinra groups, but was
8 considerably lower in the 150 mg group.

9 The six-month change, which was the
10 radiographic endpoint, is shown at the bottom. You
11 can see that the mean change was less in the three
12 anakinra groups. The placebo was 6.5, and the
13 three anakinra groups were 3.5, 4.2, and 3.9.
14 Again, no adjustment was prespecified for multiple
15 comparisons, so what I am showing here are the
16 nominal p values for the pairwise comparisons with
17 placebo, and the comparisons did not reach
18 statistical significance for any one of the
19 individual anakinra groups.

20 I would like to emphasize again that
21 because of the large amount of missing data and
22 some problems with the analysis, we would consider
23 this helpful information indicating trends, but not
24 clear evidence meeting the criteria of the RA
25 guidance document to support inhibition of

1 radiographic progression.

2 One other thing that you can see if you
3 look at the means compared to the medians for the
4 baseline is that the distribution of the data is
5 not normally distributed in that the medians are
6 considerably below the means.

7 [Slide.]

8 So, the FDA performed an additional
9 analysis using a non-parametric score, as shown
10 here. Here are the six-month change in Larsen
11 scores. For the placebo group it was 6, and for
12 the three anakinra groups it was 3, 2, and 2, and
13 the nominal p value using the Wilcoxon test for
14 each of the comparisons to placebo was as shown
15 here, each less than 0.05.

16 Again, this was not a prespecified
17 analysis, but we thought in view of the
18 non-normality of the data, it was perhaps an
19 additional helpful analysis.

20 [Slide.]

21 Amgen has presented to you an analysis of
22 the Sharp scores, which suggest the differences
23 between study arms. I would just like to point out
24 that there are some limitations to this type of
25 analysis. It is post hoc in that it was decided on

1 after the study was completed and exploratory, and
2 also that 133 fewer subjects were included in the
3 Sharp readings compared to the Sharp readings that
4 I showed you before.

5 [Slide.]

6 So, in summary, the prespecified analysis
7 of the radiographic endpoints showed trends towards
8 improved radiographic outcomes, but the results
9 were not statistically significant.

10 In addition, a post-hoc analysis also
11 suggests activity of Kineret in inhibiting
12 radiographic progression at six months, but firm
13 conclusions cannot be reached because of
14 limitations in the analysis.

15 [Slide.]

16 I am going to turn my attention now to
17 safety. The data that I will be presenting will be
18 somewhat different than the way that Amgen
19 presented to you in that I will be presenting some
20 of the individual studies rather than an overall
21 comparison of all the studies combined.

22 The number of patients exposed to anakinra
23 for varying periods of time are shown in this
24 slide, and the number of patients that we had
25 available for analysis was somewhat less than the

1 total numbers of patients who had been treated,
2 which may help explain some of the differences in
3 the total patient exposure that I am showing you
4 here compared to the numbers that Amgen showed you
5 earlier.

6 A total of 1,925 patient were exposed to
7 anakinra at doses that are at or above the dose
8 that is being proposed for licensure. The number
9 of patients treated for six months or longer is
10 1,390. We have data on 175 patients for one year
11 or longer.

12 [Slide.]

13 I am going to present the data from the
14 two, Phase III trials combined first, the deaths
15 and serious adverse events. No deaths were seen in
16 the blinded portion of these trials, and the
17 incidence of serious adverse events was similar
18 between placebo and anakinra groups in the blinded
19 portions of these studies.

20 The incidence of serious infection was 17
21 out of 1,240 on anakinra or approximately 1
22 percent, and 1 out of 243 on placebo, somewhat
23 under 1 percent. The incidence of serious
24 infection on anakinra was somewhat higher, but the
25 difference was not statistically significant.

1 The incidence of malignancy in these
2 combined trials was within the expected range, but
3 follow-up was only for six months, so to really
4 learn about the effect of anakinra on malignancy
5 will require much longer term trials.

6 [Slide.]

7 In study 145, the large confirmatory
8 efficacy trial, one death occurred on anakinra.
9 This was an 80-year-old man who had baseline
10 underlying chronic lung disease, which worsened
11 during the trial, and he died after receiving 10
12 weeks of anakinra therapy, a time after
13 discontinuing the study drug.

14 Serious infections were seen in 12
15 patients on anakinra and 8 patients in the placebo
16 arm. Three of the serious adverse events were
17 infectious in nature in the anakinra group, and one
18 in the placebo group. No malignancies were seen in
19 the anakinra arm.

20 The serious infections in the two patients
21 were two pneumonias and one that was characterized
22 as a pulmonary infection. Apart from infections,
23 no pattern of increased serious AEs was seen in the
24 anakinra group in this study.

25 [Slide.]

1 Next, I would like to discuss abnormal lab
2 values that were seen. The only laboratory
3 abnormalities that were seen were leukopenia and a
4 mild increase in eosinophil counts. Leukopenia was
5 seen in 12 percent or 85 of the 696 patients with
6 anakinra in studies 0560 and study 960180 versus 4
7 percent with placebo, or 10 out of 195.

8 I want to say that the way that leukopenia
9 is defined for these figures is an increase of at
10 least one in the grade of leukopenia. When you
11 look at discontinuation due to leukopenia, it was
12 much lower. Eight out of 696 anakinra patients
13 discontinued for leukopenia, and this was defined
14 as a white cell count below 3,500.

15 There was no specific time when these
16 events occurred. A third were in the first 100
17 days, and a third were after greater than 200 days
18 of treatment.

19 [Slide.]

20 Most of the leukopenia that was seen was
21 mild, an increase of one grade or more, for
22 example, from above 4,400 to the 3,300, to the
23 4,400 range. Two percent of the patients went from
24 normal to grade 2. This would represent a decrease
25 from above 4,400 to the 2,200, to 3,300 range. In

1 only one case in these two studies was leukopenia
2 associated with an infection. This was a
3 non-serious urinary tract infection that resolved
4 with treatment, and in this patient, the absolute
5 neutrophil count at the time of withdrawal was
6 1,800.

7 [Slide.]

8 Adverse events were seen at a higher
9 frequency with anakinra than placebo are shown
10 here. More anakinra patients had an injection site
11 reaction, 58 percent versus 26 percent. In this
12 study, 12 percent of anakinra patients reported
13 headache compared to 6 percent on placebo, although
14 this was not seen in some of the other studies.
15 Abdominal pain was seen at a slightly higher rate
16 as was rash.

17 [Slide.]

18 Next, I would like to discuss the
19 randomized safety study, study 990757. This study
20 was a double-blind, randomized, multi-center trial
21 of safety, of adding anakinra 100 mg/sub-Q/daily to
22 background anti-rheumatic medications.

23 The intention here was to get a patient
24 population that was as similar as possible to what
25 a rheumatologist might see in the ordinary practice

1 setting. So, an effort was made not to exclude
2 patients who were receiving other anti-rheumatic
3 medications and not to exclude patients who had
4 concomitant medical conditions, so long as it was
5 considered safe to do so.

6 The study took place in the U.S., Europe,
7 and Australia at 169 sites. 1,414 subjects were
8 randomized, and there was a 4 to 1 randomization
9 ratio with more patients enrolled on anakinra.

10 The data that I will be presenting is from
11 the six months of controlled therapy, and then
12 there is an additional time on open-label anakinra
13 to a total of three years.

14 [Slide.]

15 The study enrolled a patient population of
16 patients with active rheumatoid arthritis who had
17 been receiving stable DMARD regimens for at least
18 three months. Patients were not allowed to enroll
19 who had uncontrolled medical conditions or recent
20 malignancies.

21 DMARDs were allowed, and this is in
22 contrast to many other clinical trials in
23 rheumatoid arthritis. DMARDs were allowed as
24 either monotherapy or combination therapy, however
25 TNF antagonists were not permitted, either

1 etanercept or infliximab, and changes in NSAIDs,
2 corticosteroids, DMARDs were allowed as clinically
3 indicated, again, to try to reproduce ordinary
4 clinical practice and to avoid patients dropping
5 out because they can't receive the things their
6 physicians might ordinarily provide.

7 [Slide.]

8 The patients enrolled had similar
9 demographic characteristics to the other trials
10 that I have presented to you. The DMARDs that were
11 used are shown here. Approximately half the
12 patients were receiving methotrexate, 16 percent
13 were receiving methotrexate and another DMARD, 6
14 percent were receiving methotrexate and two or more
15 DMARDs, and 57 percent were receiving concomitant
16 corticosteroids.

17 We saw no imbalances in either baseline
18 disease activity or demographics between the two
19 study arms. The study did succeed in enrolling
20 patients who had serious concomitant medical
21 conditions. Between 5 and 10 percent of the
22 subjects had each of the following: COPD, a
23 history of pneumonia, asthma, coronary artery
24 disease or diabetes mellitus, so there were 5 to 10
25 percent of the patients who had each of these

1 concomitant conditions.

2 The most common anti-rheumatic medications
3 that were used apart from methotrexate include
4 hydroxychloroquine, that was used in 22 percent of
5 patients, sulfasalazine used in 14 percent, Arava
6 or leflunomide used in 10 percent, parenteral gold
7 in 4 percent, and azothiaprime in 4 percent.

8 [Slide.]

9 Eighty percent of the patients completed
10 six months of therapy. It was noted that
11 withdrawal for adverse events was more common in
12 the anakinra arm compared to placebo, 12 percent
13 versus 6 percent, and the most common adverse event
14 leading to withdrawal with anakinra was injection
15 site reactions in 7 percent of the patients, so
16 this accounts for much of the difference.

17 Withdrawal for disease progression was
18 more common with placebo, 2 percent versus 1
19 percent.

20 [Slide.]

21 Four deaths were seen in the anakinra
22 group and one in the placebo group, but recall that
23 there was a 4 to 1 randomization, so the rate of
24 mortality was less than 1 percent and approximately
25 the same in both.

1 There was a similar rate of serious
2 adverse events in both study arms, however,
3 examination of the individual serious adverse
4 events showed more serious adverse events in the GI
5 system, 2 percent versus less than 1 percent, and
6 no predominant pattern was seen in the individual
7 serious adverse events in the GI system.

8 More pulmonary serious adverse events were
9 seen in the anakinra group, 2 percent versus 1
10 percent, and the difference here was related to
11 pulmonary infections.

12 The deaths in the anakinra group were due
13 to interstitial fibrosis in one patient, suicide,
14 metastatic melanoma, and an upper GI bleed.

15 Malignancies were not observed at a higher
16 frequency in the anakinra group than placebo, but
17 recall that follow-up is only for six months, and
18 you can't reach firm conclusions about any effect
19 on malignancy until further long-term follow-up is
20 completed.

21 [Slide.]

22 Looking at infections, it was found that
23 the overall infection rate was similar between
24 study arms, approximately 42 percent in each of the
25 two arms. However, it was found that the serious

1 infection rate was higher in the anakinra group
2 than in the placebo group, as shown here.

3 Two percent of anakinra-treated patients,
4 or 23 of 1,116, had a serious infection compared to
5 less than 1 percent on placebo, or 1 in 283
6 patients. The most common of these serious
7 infections was pneumonia, cellulitis, and
8 osteomyelitis. Serious infections were defined as
9 serious infections that were infectious in nature,
10 so it's a subset of the serious adverse events.

11 [Slide.]

12 None of the serious infections in this
13 study were fatal, all resolved except one case of
14 osteomyelitis that at the time of my review was
15 ongoing. Atypical infections were uncommon. One
16 patient developed Mycobacterium
17 avium-intracellulare one month after
18 discontinuation of anakinra, and one patient
19 developed a legionella infection. None of the
20 serious infections that were seen were associated
21 with leukopenia.

22 [Slide.]

23 We carried out an extensive analysis
24 looking for potential risk factors that in
25 combination with anakinra might be increasing the

1 rate of serious infections, and the results are
2 shown here.

3 As I mentioned, the percent of patients
4 with serious infections was 2 percent in the
5 anakinra group considered as a whole. When we
6 looked at the subsets of anakinra-treated patients,
7 we found that males had a somewhat higher incidence
8 of serious infection than females, 2.8 percent
9 versus 1.8 percent.

10 Patients receiving corticosteroids had a
11 higher rate of serious infection, 3 percent versus
12 0.8 percent, and patients with pre-existing asthma
13 had a higher rate of serious infection, as was
14 discussed earlier, 5.5 percent compared to 1.7
15 percent in patients who did not have asthma.
16 Again, this is just considering the patients who
17 were receiving anakinra.

18 [Slide.]

19 The last study that I would like to
20 present was a study of Enbrel combination therapy
21 with anakinra. This is study 20000125, I will call
22 it 0125. This study was an open-label pilot study
23 of safety. It included 58 patients with active
24 rheumatoid arthritis.

25 All the patients enrolled had been on

1 Enbrel previously for at least three months, but
2 were receiving no other DMARDs. Anakinra was given
3 in doses of 1 mg/kg subcutaneously, daily, for six
4 months.

5 The mean age of the patients enrolled was
6 49. They had had rheumatoid arthritis for a mean
7 of 12 years, and the tender joint counts indicated
8 active disease, tender joint counts of 26, and
9 swollen joint counts of 17.

10 [Slide.]

11 Approximately one-third of the patients
12 enrolled in the study enrolled before the six-month
13 time point, 36 percent or 21 of the 58 patients
14 enrolled. Eleven of the patients discontinued for
15 adverse events, 8 of the patients or 14 percent for
16 withdrawal of consent.

17 There were no deaths in the study, 7
18 serious adverse events were seen. Four of these
19 were infectious in nature or 7 percent of the
20 subject enrolled, and the infectious serious
21 adverse events were two cases of pneumonia and two
22 of cellulitis.

23 One of the cases of cellulitis was
24 associated with an injection site abscess. The
25 other case was a case of facial cellulitis.

1 [Slide.]

2 Some lab abnormalities were seen in this
3 study. Five patients developed laboratory
4 toxicities defined as an increase in toxicity grade
5 of 2 or more. These were two cases of leukopenia
6 and two of lymphocytopenia.

7 Two of the cases of leukopenia occurred in
8 subjects who also developed serious infections.
9 One of these patients developed a cellulitis, the
10 other patient developed pneumonia.

11 [Slide.]

12 The time course of the calculated absolute
13 neutrophil count is shown here in the two patients
14 who developed serious infection, who also had
15 leukopenia. The first measurement is baseline, the
16 second is at one month, and the third is at two
17 months.

18 The first subject developed pneumonia 15
19 days after the second measurement, which was an
20 absolute neutrophil count of 700. Patient number
21 two, shown here, developed cellulitis 10 days after
22 the third measurement of 1,000 calculated
23 neutrophils per cubic millimeter.

24 [Slide.]

25 To provide further information about

1 serious infections in anakinra trials, I have
2 expressed the incidence of serious infections in
3 the various trials, and the 95 percent confidence
4 intervals.

5 We have combined the serious infection
6 rate in all the placebo patients in all the trials,
7 as shown here, because the rate of infection was
8 similar in all of these arms.

9 We have combined study 560 or 180 and 145,
10 because this study had similar inclusion criteria
11 one to the other. Study 990757 is expressed
12 separately because these are patients who were
13 enrolled who had concomitant medical conditions and
14 who were receiving a variety of other DMARDs, which
15 might conceivably change the infection rate.
16 Finally, the Enbrel combination study is shown at
17 the bottom.

18 What you can see is the point estimate of
19 the incidence is 0.7 percent in the combined
20 placebo arms. It is 1.5 percent in the three
21 anakinra studies, 2.1 percent in the large safety
22 study, and 7 percent in the Enbrel combination
23 study.

24 The point estimate for the incidence of
25 serious infections in the Enbrel combination study

1 was 1.9 to 17 percent, so it excluded at the lower
2 range anything below 1.9 percent.

3 [Slide.]

4 To summarize the results of the etanercept
5 combination study, the data strongly suggest that
6 there may be a somewhat higher incidence of serious
7 infections when anakinra is given with etanercept.

8 Concurrent leukopenia was observed before
9 serious infection in two of the patients. Finally,
10 the widespread use of TNF antagonist etanercept and
11 infliximab raises concerns that they be used in
12 combination with anakinra if it is approved, and
13 raises concerns about whether the incidence of
14 serious infections and leukopenia might be higher
15 in this combination than was observed in the other
16 studies as anakinra.

17 Also, I would like to note that the
18 experience that is available at the current time on
19 combination therapy with etanercept is quite small,
20 only 58 patients were enrolled in a six-month
21 study, so we can't really make firm conclusions
22 about the safety of combination therapy.

23 [Slide.]

24 In conclusion of the safety evidence that
25 I have presented to you, the majority of patients

1 treated with anakinra developed mild to moderate
2 injection site reactions. A minority of patients
3 developed low grade leukopenia. A higher incidence
4 of serious infections were seen in one large trial.

5 I have raised concerns about the safety of
6 use of anakinra in combination with TNF
7 antagonists, and I would note that we don't have
8 any information on its combination with infliximab.

9 Finally, although anakinra was generally
10 well tolerated, long-term safety has not been
11 assessed, although studies are in progress.

12 Thank you.

13 DR. HARRIS: Dr. Brandt.

14 DR. BRANDT: Perhaps I missed this, but in
15 your subsetting, as you looked at signs and
16 symptoms, did you look at x-ray severity at
17 baseline, and did you look at duration of
18 rheumatoid disease?

19 DR. JEFFREY SIEGEL: Yes. I can't
20 remember if I showed you the data on the duration
21 of rheumatoid arthritis, but we did subset it based
22 on the people with longer versus shorter in each of
23 the studies, and an increase in ACR20 responses
24 were seen in both subsets.

25 In terms of the baseline x-rays, I don't

1 recall that we subsetted that.

2 DR. HARRIS: Dr. Abramson.

3 DR. ABRAMSON: Jeff, in the risk factors
4 for infection when you looked at asthma patients
5 and steroids, were they independent risk factors,
6 specifically, in asthma patients, was steroid dose
7 controlled for?

8 DR. JEFFREY SIEGEL: When corticosteroid
9 use emerged as a potential risk factor, I looked in
10 great detail at the use of corticosteroids. One
11 think I looked at was whether the serious
12 infections were associated with a dose of
13 corticosteroids above 10 mg of prednisone. They
14 were not.

15 There was some use of a dose of prednisone
16 above that, but it was exclusively in patients who
17 had a flare of COPD or asthma, and in no case was
18 it associated with serious infections.

19 So, essentially, all of the corticosteroid
20 use was 10 mg of prednisone or below.

21 DR. ABRAMSON: But, specifically, was
22 asthma an independent risk factor when you
23 controlled for concomitant steroid use?

24 DR. JEFFREY SIEGEL: That is a good
25 question, and I don't think we did that analysis.

1 DR. HARRIS: Dr. Anderson.

2 DR. ANDERSON: I have a question about the
3 x-rays in study 0560. On page 46, Table 26, I am
4 not sure whether this is that there were 74 percent
5 and numbers in that sort of range of patients on
6 whom you had x-ray data or whether that is the
7 percentage who actually had erosions and that a
8 quarter of them didn't have any erosions at
9 baseline, and if there were some without erosions,
10 have either the FDA or the sponsor done any
11 analyses of whether they stayed free of erosions at
12 the 24-week follow-up.

13 DR. JEFFREY SIEGEL: I don't think that we
14 have done extensive analysis of that although I
15 agree it is an important question.

16 DR. HARRIS: Okay. Sponsor?

17 MS. BEAR: Could we bring up slide R811a.

18 [Slide.]

19 To get at your question, what we did is we
20 actually did analysis where we put all patients in
21 for the Larsen score. If a patient showed no
22 disease progression, we counted them as a
23 non-progressor. If the showed a progression, that
24 would be a positive change from baseline, we put
25 them in, and if a patient dropped out, we assumed

1 that they were a progressor.

2 You can see here in terms of the
3 anakinra-treated patients, the proportion of
4 patients that showed no further disease
5 progression, if you will, over the 24-week
6 treatment period.

7 DR. ANDERSON: That is related, but not
8 quite the same. Just another question, I was
9 wondering, I know the Sharp scores weren't part of
10 the primary analysis, but why were there so many
11 fewer x-rays available for Sharp scoring?

12 MS. BEAR: In terms of those x-rays
13 included in the analysis, there actually was not, and
14 if I could bring up slide R892.

15 [Slide.]

16 This shows the radiographic disposition
17 for both the Larsen and Sharp scores that were
18 included in the 24-week analysis. We can see here
19 that for the placebo groups and the anakinra groups
20 in both the Larsen score, the numbers are only
21 slightly different from that seen in the Sharp
22 scores for placebo and anakinra, and the small
23 differences that we see here is primarily because
24 the radiographs had to be retrieved once again from
25 the sites, and we had difficulty sometimes

1 retrieving those x-rays.

2 In addition, for the Sharp score, they
3 were read in pairs, so if we only retrieved a
4 single x-ray, they were not included in the
5 analysis and they were not read. Some of the
6 discrepancy may be because in terms of just the
7 baseline radiographs, in other words, if we just
8 had a baseline radiograph for Sharp, we didn't
9 bother reviewing it because again, the method
10 required at least two x-rays.

11 For the Larsen score, however, everybody
12 was required to have a baseline x-ray, but in terms
13 of who was included in the analysis, the numbers
14 are very comparable.

15 DR. JEFFREY SIEGEL: I think the
16 differences may be between the number of films that
17 were read versus the number that were included in
18 the analysis was an imputation method used for the
19 missing values, because this was noted.

20 DR. WOFSY: I wonder if you could clarify
21 for us a bit the thinking behind the decision to
22 suggest an uncontrolled trial of the combination of
23 etanercept and anakinra. It is clear that this was
24 an important topic for the FDA, you asked for this
25 work, and it is clear from Dr. Perlmutter's

1 presentation that the potential for combining these
2 agents is central to the way the sponsor thinks
3 about these two agents.

4 Now we have an uncontrolled experience
5 with a somewhat concerning high serious adverse
6 event profile. Give us a little of the background
7 of how this particular design was decided on and
8 what you would propose that we do with it.

9 DR. JEFFREY SIEGEL: The issue of the
10 safety of combination of new agents with other
11 agents is a very important one, and it is only
12 going to become more and more complicated as new
13 agents with new mechanisms of action are approved.

14 Currently, the FDA does not require for
15 licensure, there is not a formal requirement for
16 exhaustive safety information on every combination.
17 We, at the Center for Biologics, are strongly
18 encouraging extensive data collection on
19 combination with methotrexate because at the time
20 that these studies were done, that was the standard
21 of care, and now that TNF antagonists are being
22 used more and more widely, we have become concerned
23 about combination use with these agents, as well,
24 but we have not formulated an absolute requirement
25 for extensive data on these combinations before

1 approval.

2 So, the way the particular study design
3 was reached was we asked the sponsor to collect
4 some data on combination therapy at the time of
5 submitting a BLA, so that we could consider that.

6 Ordinarily, if there are concerns, safety
7 concerns in particular, sponsors like to do pilot
8 studies first that are open label, to help them
9 design subsequent randomized trials that will
10 provide more definitive efficacy data.

11 Amgen decided that the study that they
12 would do first was an open-label study, and you
13 will have to ask them in more detail about their
14 decisionmaking process.

15 We certainly agree that a randomized trial
16 is necessary for getting definitive information on
17 safety, and that is something that we are very
18 interested in the committee's comments on, about
19 where you think that fits in the general scheme of
20 things.

21 DR. SCHWIETERMAN: Dr. Harris, if I may
22 just add on to that. Dr. Wofsy, actually, you are
23 probably aware this is actually an important
24 question we are asking the committee this
25 afternoon, and I think to be honest with you, that

1 the field of rheumatology is advancing so quickly
2 that the questions that we are asking of sponsors
3 now involve many, many things, and I think the
4 standards for combination therapy maybe have fallen
5 behind some of the other things that we have asked
6 about - monotherapy, radiographic progression,
7 durable response rates, that sort of thing.

8 It is very clear, I think, that the Agency
9 now recognizes that combination therapies are going
10 to be likely with many of the new therapies coming
11 down the road, so what we are seeking from the
12 committee this afternoon is specific guidance on
13 the kinds of numbers and the kinds of trials that
14 are required because clearly this is an important
15 question.

16 DR. PERLMUTTER: David, let me just speak
17 to the question you raised. I think it is an
18 important one. As Dr. Schwieterman has indicated,
19 the field has been evolving rapidly, and as you
20 well know, in terms of the design of clinical
21 trials, there is reason to believe on the basis of
22 preclinical studies, some of which I described,
23 that because of the fact that an interleukin-1
24 antagonist works by a related but different
25 mechanism from a TNF sequestering, that the two of

1 them might possibly interact, and because there is
2 synergy in preclinical experiments when those two
3 are administered together, it is possible that
4 ideal therapy would involve dose adjustment of
5 both.

6 That makes for a pretty complicated
7 clinical study as you can imagine. Our concern was
8 that we wanted to bring forward anakinra for the
9 benefit of patients and, at the same time, as we
10 didn't want to compromise the ability to use this
11 therapy in those who were refractory to other
12 therapies, and at the same time, we wanted to be
13 sure, since it might happen that it would be used
14 in combination with anti-TNF therapy, although that
15 was not the intention, we wanted to get some
16 initial read as to whether or not that would not
17 turn out to be safe. That was the design of an
18 open-label study, just to get that kind of
19 information.

20 A much more detailed study, in fact,
21 several more detailed studies will be required in
22 order to understand how these two could be used in
23 combination if, in fact, that turns out to be
24 valuable.

25 Certainly, we are encouraged by the

1 observation that people on stable anti-TNF therapy
2 seem to experience some benefit when they were
3 given anakinra, but clearly, we have to do much
4 more in order to understand how to use these
5 together, if they were going to be used together.

6 DR. HARRIS: Dr. Felson.

7 DR. FELSON: The infection issue has I
8 think reared its head, and you showed some data on
9 rates of infection in placebo, and then various
10 other groups in various trials.

11 They were incidence rates per person,
12 Jeff, and I am wondering if those were patients
13 followed for equal amounts of time on each of those
14 regimens, and if that is a person/time computation,
15 which I think would be more helpful to us.

16 DR. JEFFREY SIEGEL: We talked about that,
17 and I would agree if you have greatly differing
18 duration of exposure, it is important to adjust for
19 that. For this particular data, all of the
20 studies, the patients in both arms were exposed to
21 placebo or anakinra for comparable periods of time.

22 So, if we were to adjust for the time on
23 drug or placebo, it wouldn't change the figures
24 very much.

25 DR. HARRIS: No other comments, questions?

1 Okay. Thank you very much.

2 We are moving into the public hearing
3 portion of our session. Is there anyone wishing to
4 make any public comment?

5 Mr. Richard Van Antwerp.

6 Open Public Hearing

7 MR. VAN ANTWERP: My name is Richard Van
8 Antwerp. I am a native of California. I have a
9 background in the Navy, I retired from the Navy in
10 1975 and returned to California, and then promptly
11 came down with rheumatoid arthritis. I am not sure
12 of any correlation there, whether I retired too
13 young or whether it was California's welcome back
14 after the Southeast Asia conflict.

15 In any event, my rheumatoid arthritis
16 started about 12 years ago. At that time, I went
17 to the UCLA School of Medicine, Rheumatology
18 Department, where I was diagnosed after a period of
19 time of rheumatoid arthritis.

20 Then, I started into the more conventional
21 treatments, the hierarchy of the prednisone,
22 plaquenil, sulfazide, Imuran, and then
23 methotrexate. I was doing okay, but I was always
24 afraid of the pain, and I had the swollen joints
25 and the fingers.

1 My wife and I decided--at the time we were
2 living in the Santa Barbara area on the coast,
3 where I was born and raised--and we decided to move
4 to the desert where perhaps the hot weather and the
5 dry climate would be of some assistance.

6 We moved down there, to make a long story
7 short, and retired to the 13th green of a golf
8 course country club, and at that time I would go
9 out on the golf course, my wife would tee off and
10 drive, and then I would do the chipping and
11 putting, and that seemed to be what I was going to
12 be destined to do for many years.

13 It is kind of a vicious circle. I knew I
14 needed more exercise, and I felt better when I got
15 more exercise, but the pain wouldn't permit the
16 more exercise, so it was just kind of a downward
17 spiral. Mentally, it was really debilitating, as
18 well as physically.

19 At that time, I was referred to a
20 rheumatologist in the desert, Rancho Mirage, Dr.
21 Maria Greenwald, who was affiliated with Amgen and
22 her studies. I was in one study initially, and
23 then about a year ago, was brought into the
24 anakinra study, Kineret.

25 After, I think it was about three to four

1 months on anakinra and methotrexate, I felt so good
2 and just unconsciously started going things that I
3 couldn't do and hadn't been able to do in the past.

4 So, we decided, well, it was time to
5 continue life, so we went up into Northern
6 California just outside of Yosemite, and bought a
7 ranch, which we always wanted, and started
8 rebuilding the ranch, which had not been occupied
9 for a number of years.

10 So, I have just restarted my life thanks
11 to anakinra as far as I am concerned. I don't have
12 the swollen joints, I don't wake up with the
13 morning stiffness anymore, I got rid of that about
14 three or four months ago, and mentally, I am back
15 and ready to go to work.

16 Thank you.

17 DR. HARRIS: Thank you so very much for
18 your comment.

19 Mrs. Diane Van Antwerp.

20 MRS. VAN ANTWERP: Okay. You are all so
21 learned and everything, and we are so impressed and
22 so grateful for Amgen, we really are. I would like
23 to thank Amgen, I would like to express our
24 appreciation to the FDA also.

25 Let me say two things, first of all, that

1 Dick and I are together 24 hours a day, 7 days a
2 week, so I am kind of a good judge of Dick. He has
3 no signs whatsoever of any side effects at all.
4 This ranch that we purchased is 20 acres,
5 significant.

6 It is significant because at the time the
7 remarkable effects of Kineret transferred him so
8 fast, and with such endurance and with such
9 strength, that it enabled him to do things that
10 most men in this room may not be able to do.

11 We also commute back to Santa Barbara. We
12 commute there, that is like five hours. We spend
13 about 10 percent of our time because we have
14 another home there. So, we go back and forth, and
15 takes a lot. Before, Dick couldn't even grasp the
16 steering wheel, you know, that really hurt to drive
17 those long distances, so not anymore, so he drives
18 the whole way now.

19 Now, like after Kineret, he just jumps
20 into things spontaneously, and that is significant
21 for you, too. It is not as measured as what it
22 seems up on that screen. That is so wonderful to
23 know and to see what you all do, and what you all
24 know, but it is a little bit more spontaneous what
25 that medicine has done to Dick.

1 Before, we just took it like one day at a
2 time, and I think out of the obvious pain that Dick
3 had, one of the more significant things that really
4 was important is his loss of independence, and that
5 probably at times hurt a lot more than the real
6 pain itself, because there would be so many things
7 that Dick would want to do for me, for us, and he
8 just couldn't. He would start to do something, and
9 we would start to plan a day, and we had all these
10 great plans, and then, you know, bam, it hurt, and
11 it hurt fast, and it hurt for a long time, so we
12 had to recover.

13 So, you regroup and you regroup, and your
14 life is very measured.

15 Now, Dick has like a life without
16 boundaries. He has cut down 12 oak trees, he has
17 put up 3 acres of fences. He makes pens for our
18 animals. This is 20 acres, and that is a lot. We
19 completely redid the whole house. He has done all
20 the irrigation by hand because they told us it
21 would be \$8,000, and Dick said he could do it for 100.
22 So, he is doing it, but he is up and down, on his
23 knees all the time, and I can actually see all of
24 his knuckles. That is a big deal, big deal.

25 He shovels rocks and he otherwise just

1 does what he darn well feels like doing at any
2 time.

3 The study group that we were in with Dr.
4 Greenwald was meticulous. I mean they would just
5 count every single toe over and over again. They
6 were always just fussing over him and just
7 everything and anything.

8 I went in with him, and it is good, it was
9 good it was so meticulous. Amgen must have ordered
10 they want it by the letter, up one side and down
11 the other, I don't know, but it was really good.

12 Then, I guess important, too, was sometime
13 ago he said to me that he doesn't think now about
14 doing things. It was interesting to him. He said,
15 "I don't even think about doing things anymore, I
16 just kind of like go do them."

17 So, his endurance is I guess I need you to
18 understand that his endurance has just
19 sky-rocketed, and his strength, he is very, very
20 strong. His independence is intact, and probably
21 one of the best gifts that Amgen's Kineret has
22 given us is Dick's enthusiasm back, enthusiasm to,
23 you know, go jump into anything.

24 I think when Dick got with Kineret, he
25 just took off, you know, have you ever been like in

1 a 747, you know, it is just getting ready to go on
2 the runway, and you can feel, you know the power is
3 there and everything? Well, that is kind of how
4 Dick took off with Kineret.

5 I mean he just took off like an
6 impassioned 747, and he is really doing good. So,
7 thank you very much, Amgen and the FDA for
8 overseeing this.

9 Thank you.

10 DR. HARRIS: Thank you so very much.

11 The final comment is from Ms. Shelly
12 Romero.

13 MS. REEDY: I will speak for Ms. Romero.
14 Ms. Romero is a rheumatoid arthritis patient that
15 was also in a Kineret trial, who registered to
16 speak today, and she was out riding a scooter with
17 her son, and that probably covers what she wanted
18 to say to us, but had an accident and was spending
19 the day with an orthopedic surgeon for a fracture.

20 DR. HARRIS: I don't know what comment one
21 makes.

22 MRS. ANTWERP: May I say one more thing,
23 sir? Just one more thing. There is one side
24 effect to Dick, and that is because of what you all
25 did, he got me my own chain saw.

1 DR. HARRIS: Well, on that note, thank you
2 very much.

3 Would you like to make a comment?

4 MS. MALONE: Yes, I would. I would like
5 to thank the patients for speaking up. One would
6 hope that this therapy would help everyone as much
7 as it does you.

8 Now, this is anecdotal, of course, and not
9 everyone will have the same reaction, but I think
10 what the speakers have said has brought out the
11 idea that rheumatoid arthritis is not just a
12 disease of the body, it's a disease of the mind,
13 emotions. It affects you psychologically, it
14 affects your family, it affects the work force,
15 which affects our economy, and that is the reason
16 that we are all here, because we want to do
17 something about the disease to add to the quality
18 of life and actually to put ourselves out of
19 business.

20 DR. HARRIS: Thank you. That was an
21 appropriate closing remark.

22 We are going to break for lunch. We are
23 going to reconvene at 1 o'clock. Thank you.

24 [Whereupon, at 11:45 a.m., the proceedings
25 were recessed, to be resumed at 1:00 p.m.]

1 AFTERNOON PROCEEDINGS

2 [1:00 p.m.]

3 DR. HARRIS: Let's start the afternoon
4 session.

5 In this session, as you know, we are going
6 to address a series of questions that were posed to
7 us by the FDA. The way in which I will do it is
8 each question, I will first call on one or two
9 members of the committee to comment, and then we
10 will move on and have general comments later.

11 I will ask that all keep their remarks
12 brief. We are going to try to give as much
13 discussion, but at the same time, would like to
14 finish in a timely fashion this afternoon.

15 Discussion and Questions

16 DR. HARRIS: I am going to read the first
17 question. There may have been some changes, but
18 they are minor.

19 The first question regards safety in the
20 absence of TNF agents.

21 The question reads: Patients receiving
22 anakinra in the absence of anti-TNF blocking agents
23 experienced a 3-fold higher rate of leukopenia
24 across all studies, 12 percent on the agent
25 anakinra (with a 95 percent confidence interval of

1 9.9 to 15 percent) versus 5 percent placebo, and
2 the confidence interval is there, a higher rate of
3 serious infections in one study, 2.1 percent with
4 anakinra versus 0.4 percent with placebo, and
5 frequently, injection site reactions.

6 Although nearly 2,000 patients have been
7 treated with anakinra, only 175 have received the
8 product for one year or longer.

9 Please discuss these safety data,
10 particularly with regard to--and we will start with
11 Question No. 1--the size of the safety database.

12 1. Has the sponsor studied an adequate
13 number of patients to support the safety of
14 anakinra for the treatment of rheumatoid arthritis?

15 I want to first start by posing this
16 question to Dr. Jennifer Anderson just to comment
17 about the database, comment generally about some of
18 the statistics here and some overall comments about
19 the study itself, and then I am going to ask Dr.
20 Elashoff to follow.

21 DR. ANDERSON: I am addressing the
22 question of the size of the database and whether
23 that is enough for decide on whether the agent is
24 safe or not. Is that what you would like me to do,
25 or to address the--I will confine myself to that.

1 DR. HARRIS: Has there been an adequate
2 number of patients to support the--

3 DR. ANDERSON: --safety, yes.

4 DR. HARRIS: Right.

5 DR. ANDERSON: Well, I believe that the
6 guidelines only require 2,000, or it is suggested.
7 I don't have the guidelines here to be absolutely
8 sure. Is that correct?

9 One would always like there to be more
10 patients studied, so that you can be more sure
11 about safety, and the fact that there are only 175
12 who received it for a year or longer means that
13 safety studies, I would say are incomplete at this
14 point. I don't think I can say more than that.

15 DR. HARRIS: Thank you.

16 Dr. Elashoff.

17 DR. ELASHOFF: In terms of whether a
18 safety database is large enough, it depends on what
19 size event rate you are trying to rule out, so that
20 with a safety database of only about 100, you can
21 easily have event rates of 1 or 2 percent, and not
22 have seen any in the hundred.

23 So, from that point of view, it is easy to
24 specify what kind of event rates you want to be
25 able to rule out if you haven't seen them, and say

1 what size the safety database ought to be for that
2 purpose.

3 DR. HARRIS: Thank you.

4 I am going to ask Dr. Felson to comment
5 and then we will open for general comments.

6 DR. FELSON: I think because they did a
7 safety trial and because the rates of occurrences
8 of adverse events, serious adverse events like
9 serious infections and, in addition, the rates of
10 injection site reactions seem to be comparable
11 across the various studies they did, I feel that
12 there is probably enough safety data to think
13 about, to have a reasonable sense of what the
14 likely common side effects and problems are here.

15 Number one, they have got a large trial
16 that is safety oriented, that really does provide
17 useful information, and, number two, there are
18 consistent results across these studies, and I
19 think those both things that give more confidence
20 or narrow the confidence down to actually around
21 each of these event rates.

22 I think they suggest that there is a
23 higher rate of serious infections than would
24 otherwise be expected especially pneumonias, and
25 injection site reactions are common, and I am not

1 sure that additional data on those matters are
2 needed.

3 I think if there were a rare event that we
4 were very concerned about, we would need more. I
5 think if we were especially concerned about
6 malignancy, there is not enough data here to
7 evaluate that. It is not because there aren't
8 enough patient years, it is because there isn't
9 long enough follow-up. Those things happen over
10 longer periods of time.

11 DR. HARRIS: So, you are comfortable that
12 enough patients have been studied long enough to
13 give some sort of comfort level about the results
14 we are seeing?

15 DR. FELSON: Yes.

16 DR. HARRIS: I am going to open now for
17 general discussion of the committee. Dr. Williams.

18 DR. WILLIAMS: I would agree entirely with
19 Dr. Felson. I think we have enough safety data for
20 this point. The rest of it will have to come with
21 postmarketing surveillance after you see thousands
22 of patients and millions of doses.

23 DR. HARRIS: Does anybody on the committee
24 feel differently?

25 [No response.]

1 DR. HARRIS: Fine. Then, we will push on
2 to Question No. 2.

3 The second question involves the incidence
4 of leukopenia. Were anakinra to be approved, what
5 precautions or guidance should be included in the
6 package insert for monitoring of leukopenia?

7 I am going to start with Dr. David Wofsy.

8 DR. WOFSY: Well, I will open it for
9 discussion rather than trying to give a precise
10 answer, because I think this is an issue we should
11 have some back and forth over.

12 I think to sort of open the discussion, I
13 would say that it is an issue of significant
14 importance in the data that has been accumulated,
15 so that it should be addressed in the instructions.
16 There should be guidance on this issue, and it will
17 require some regular monitoring, the frequency of
18 which I would like to sort of see us open for
19 discussion at this point.

20 I think it is reassuring in general terms
21 that there wasn't a close correlation between the
22 occurrence of leukopenia and the serious infectious
23 adverse events that occurred, that the leukopenia
24 was reversible, and not progressive, and I think
25 that needs to be taken into account. This is a

1 manageable, in my view, a manageable adverse event,
2 but will need monitoring.

3 DR. HARRIS: Let me just throw another
4 question to you, and then we will go again. How
5 frequently would you monitor blood counts, if you
6 were the treating physician, how would you
7 recommend at least?

8 DR. WOFSY: I will answer it directly, but
9 the reason I shied away from it is I think in the
10 early stages of a new agent being on the market,
11 people have somewhat different styles, and it is my
12 style to err on the especially cautious side, but I
13 am not sure that that should be instructed of
14 everyone. That is why I am hesitating.

15 So, yes, if it were myself with a new
16 agent, where we knew this was toxicity, I would
17 almost certainly in the early stages of initiating
18 this form of therapy, want to be looking at counts
19 monthly.

20 DR. HARRIS: Other comments? Dr.
21 Williams.

22 DR. WILLIAMS: I agree. I think that the
23 white count drops we saw are, in general, only
24 moderate, and I agree, I am comforted by the fact
25 there was not a close correlation with infection.

1 I hate to increase the cost of a drug by a
2 lot of monitoring. I would probably recommend
3 monthly for three months, then, quarterly.

4 DR. HARRIS: Dr. Brandt.

5 DR. BRANDT: I think that with a new
6 agent, especially one that is likely to be used in
7 the presence of other agents, which may in
8 themselves cause leukopenia, it is reasonable to
9 provide some direction, and monthly sounds
10 reasonable to me.

11 DR. HARRIS: Does anybody feel any sense
12 of alarm about the degree of leukopenia or the
13 amount we are seeing here? In other words, is
14 there something specially we should do?

15 DR. WILLIAMS: When you say "alarm," we
16 already use a lot of agents that cause leukopenia,
17 so we are used to monitoring for it, and I don't
18 know that I find this any more alarming than any of
19 the other agents we use.

20 DR. ABRAMSON: I was wondering how much we
21 know about what causes the leukopenia from
22 preclinical studies. I don't know whether the
23 sponsor has any insights, are there bone marrow
24 issues going on or in animal studies, for example,
25 or is this purely coming out at clinical trials?

1 DR. HARRIS: Dr. Perlmutter.

2 DR. PERLMUTTER: Let me just address it in
3 general terms, that it is well known from
4 administration of IL-1 in preclinical species that
5 it causes white cell immigration from the marrow,
6 and so it increases white counts.

7 It is also well known, as we described, as
8 everyone I think on this panel knows, that an
9 elevated white blood cell count is associated with
10 inflammatory disease, so it is in a sense to be
11 expected, and it is routinely observed in the
12 preclinical environment that when you give
13 interleukin-1 receptor antagonist, that white cell
14 counts drop, in part because you are dropping the
15 IL-1 drive that increases white blood cell counts.

16 Now, you can't say in any individual
17 patient how much of the steady state white cell
18 count is reflective of the IL-1 effect that is
19 ongoing in that patient, and I think what we are
20 seeing in our clinical studies is a variability in
21 terms of how much of that we remove.

22 But there are some who have argued, some,
23 in fact, within our expert consulting group, who
24 have argued, gee, you know, this drop in white cell
25 counts is just normalizing the white cell count

1 from its apparent elevation.

2 I take the view that, in fact, there is a
3 component of IL-1 drive for white cells, and that
4 you are going to see some reduction in white cell
5 counts, and from our perspective, that is something
6 that is worth paying attention to, just as Dr.
7 Wofsy said.

8 If I may take this moment from a safety
9 perspective to make plain that there is agreement
10 between the sponsor and the FDA in terms of how
11 much safety data has been accumulated, and, in
12 fact, there were a total of 273 patients who were
13 exposed for one year or more to 100 mg of drug or
14 more. So, there is I feel a larger safety database
15 than was indicated in that question. Dr. Siegel
16 could respond to that.

17 DR. HARRIS: Thank you.

18 Dr. Katona.

19 DR. KATONA: Along the same lines, I would
20 like to ask the sponsor whether they have any data
21 on the patients who are getting infected with
22 something, whether they--leukocytosis, what is
23 their response, and how the drug interferes with
24 that.

25 DR. BEKKER: Your question, if I

1 understand correctly, is whether IL-1ra would
2 interfere with the leukocytosis response. We have
3 not systematically looked at that, but we did
4 notice when we look at individual patients of
5 interest with infections, that many of them have an
6 increase in their leukocyte counts at the time of
7 the infection, so even though we haven't formally
8 analyzed that data, at least anecdotally, we don't
9 see any evidence of that.

10 DR. HARRIS: Dr. Wofsy.

11 DR. WOFSY: If we are sort of rounding up
12 on No. 2 here, I will raise another point that is
13 inherent in the discussion of No. 2, and perhaps it
14 hasn't come up because no one feels that we should
15 address this issue in warning, but there are two
16 questions. One is how frequently the white count
17 should be monitored, and the other is whether there
18 is a level beneath which this agent shouldn't be
19 initiated.

20 That is a challenging question in
21 rheumatology in general because oftentimes people
22 are neutropenic or leukopenic either as a
23 consequence of therapy for active disease, or as a
24 consequence of some component of the disease
25 itself, and sometimes that leukopenia responds, so

1 in some of the sicker patients, we see neutropenia.

2 That is less common certainly in
3 rheumatoid arthritis, but it is not hard to imagine
4 a situation in which combination of disease and
5 therapy might, as did in looking at the subjects
6 who were candidates for this trial, neutropenia
7 might occur in a patient where you were considering
8 this agent and frankly wondering if the beneficial
9 benefits of a new agent might be result in
10 ameliorating the disease and allowing the counts to
11 come up.

12 So, my own view, that is, by raising a
13 question only to dispense with it from a personal
14 point of view, is I don't think there should be an
15 absolute restrictive level of white count beneath
16 which we wouldn't initiate this drug, but I did
17 think it is worth at least a moment of pausing to
18 think about that aspect of this issue, as well, not
19 just the monitoring aspect.

20 DR. HARRIS: Is there any comment?

21 DR. JAY SIEGEL: You posed a question
22 about how profound the leukocytosis was or wasn't.
23 It is my understanding of the design of the study
24 that patients were monitored and generally, when
25 the white count got to, what, 3,000 or 3,500, drug

1 was stopped.

2 So, one wouldn't know whether one might
3 see more profound leukocytosis if a physician
4 didn't monitor as aggressively, say, as Dr. Wofsy
5 indicates he likes to.

6 DR. BEKKER: Just to make a statement on
7 that, in the early studies, as I pointed out, there
8 was a protocol-mandated withdrawal, but in the
9 large safety study, and the confirmatory efficacy
10 study, we did not have that protocol-mandated
11 withdrawal.

12 In terms of the inclusion/exclusion
13 criteria, we did exclude patients with a neutrophil
14 count below 1,000 in terms of entry into the study.
15 So, in the large safety study, we did have
16 opportunity to fully evaluate the change seen with
17 anakinra.

18 DR. HARRIS: Dr. Williams, let me pose
19 this question a little differently. What sort of
20 guidance would you recommend in terms of utilizing
21 this agent with respect to leukopenia?

22 DR. WILLIAMS: I think like with a lot of
23 other agents, we teach the physicians that there is
24 a risk of leukopenia, and that leukopenia may be
25 associated with severe infections, and then give

1 some guidance as to monitoring. I was a little
2 more lenient than David in that I would have done
3 it initially regularly, and then I would go to a
4 little less regularly, just because it is still
5 relatively uncommon.

6 DR. HARRIS: To the FDA, do you think that
7 you have enough out of this question so far?
8 Presumably, you have got sort of guidance that you
9 normally give agents in which leukopenia might be a
10 risk.

11 DR. SCHWIETERMAN: Let me summarize and
12 then the committee members can tell me if I have
13 summarized accurately. I have heard that there is
14 no perhaps strict contraindication for a particular
15 level leukopenia for this particular product that
16 you are all recommending for the package insert,
17 but that the general consensus is that there ought
18 to be monitoring perhaps more aggressively earlier
19 rather than later in a guidance sort of way, in
20 other words, not some sort of strict regimen, but
21 in other words, guidance that physicians can base
22 their decisions on.

23 I don't know if that is accurate or not.

24 DR. HARRIS: I think that captures it, but
25 I should ask, is there some sort of level of white

1 cell count below which perhaps one should not use
2 the agent?

3 DR. ABRAMSON: I don't think, in terms of
4 that question, Nigel, other than giving broad
5 guidance, that there should be a number. I think
6 David expressed it pretty well, it is kind of a
7 clinical judgment in my view, because the disease
8 itself may be contributing to the leukopenia.

9 I would think I would do more than
10 guidance. I would give some specific
11 recommendations, I think was the sense of the
12 committee, perhaps somewhere, Jim had monthly and
13 then quarterly, and I am not sure where we would
14 come in between those numbers, but I would give
15 some specific benchmarking to people, so that it
16 doesn't become perhaps lost in some physician's
17 desk.

18 DR. SCHWIETERMAN: Just parenthetically,
19 it is likely following this discussion, we will go
20 back to the clinical trial data themselves,
21 summarize that in the package insert, and then
22 provide guidance based upon the data that have
23 already been generated, and then specifically about
24 what physicians ought to do because of that.

25 DR. HARRIS: Is that satisfactory? Okay.

1 Let's push on.

2 We have gotten a new yellow sheet. The
3 risk of serious infection with the use of anakinra
4 in the absence of anti-TNF blocking agents, are
5 additional studies needed to further characterize
6 this risk? If so, what types of studies should be
7 conducted?

8 Anybody want to take a shot at that?

9 DR. WILLIAMS: I think we have these same
10 similar risks. I think we see that we have similar
11 risks with this agent as we have with many of the
12 other agents we use, and what we have already
13 discussed would be appropriate just to identify
14 that those risks are also present here. I don't
15 think further studies are needed.

16 DR. ABRAMSON: I would agree. I would
17 also add that there are subpopulations that I think
18 we need more information about as data is
19 collected. There is the issue of the asthma,
20 whether that is related to steroid or separate, the
21 comorbidities, I am not sure we have enough
22 information to know about diabetes, I mean the
23 usual kinds of things that I think we need more
24 data on, elderly populations, I am not sure we have
25 seen enough subset analysis.

1 I say that only in the context of what Jim
2 is saying, that this drug appears to have a
3 profile, you know, comparable to other DMARDs that
4 we use, but those are issues that I think just need
5 to get looked at going forward, not to prevent any
6 decision for registration, but I think they are
7 missing data currently.

8 DR. HARRIS: Other than it is out of phase
9 4 monitoring, do you think that it rises, the
10 concern rises to the level of actually conducting
11 further safety trials to determine that?

12 DR. ABRAMSON: No, I don't think so. I
13 think those are just still open issues that we need
14 more clarity on, but not to require most studies
15 specifically.

16 DR. HARRIS: There seems to be a consensus
17 around the table, unless somebody has any other
18 sort of burning comment to make. So, I guess the
19 sense here is that there doesn't seem to be a need
20 for further study to characterize risk, but I guess
21 everybody would certainly want Phase 4 monitoring
22 and, or course, certainly particular attention
23 played to the subsets of patients that were
24 mentioned previously.

25 DR. SCHWIETERMAN: Just to comment briefly

1 with the revised questions. The yellow sheet
2 actually is a revision that we have just generated
3 that replaces certain inaccuracies and changes a
4 few of the questions. For the audience, it follows
5 the general format, but I just want to make it
6 clear why this version was here. There were some
7 typos and corrections necessary.

8 DR. HARRIS: Thank you.

9 We will go to the second question which
10 regards safety and efficacy. Anakinra was shown to
11 provide higher ACR20 response rates than placebo in
12 a large randomized controlled trial, 38 percent
13 versus 22 percent respectively, with a p value as
14 shown. Clinical data from other smaller randomized
15 studies was also supportive of the clinical
16 efficacy of anakinra. Relatively few patients
17 experienced ACR50 responses, 17 percent in the
18 agent versus 8 percent placebo, or ACR70 responses,
19 6 percent anakinra versus 2 percent placebo.

20 So, the question is: Please discuss the
21 efficacy data, particularly with regard to the
22 relatively few ACR50 and ACR70 responses when
23 compared to placebo. Given the overall benefit
24 (absolute 10 to 16 percent higher ACR response
25 compared with placebo response and smaller amounts

1 of difference with regard to ACR50 and 70) and a
2 potential increased risk of serious infection
3 (5-fold in one study), do these data demonstrate an
4 appropriate safety and efficacy profile of anakinra
5 as a treatment for rheumatoid arthritis?

6 It is a long question, but I think the
7 sentiments are clear. I thought I would
8 start--well, Dr. Felson.

9 DR. FELSON: I am troubled by--first, I
10 think this question perhaps ought to be a part of
11 the first question, but that's another story. The
12 data presented to us this morning suggest a very
13 modest efficacy profile, 10 to 20 percent better
14 than placebo.

15 Most of what we have recently released for
16 rheumatoid arthritis has substantially better
17 efficacy than this. This is not a very strong
18 therapy. It is also fairly dangerous therapy. I
19 think Jim was right in commenting that it is not
20 dissimilar probably from some therapies we already
21 have.

22 I mean I think the issue here is not
23 whether it's efficacious, we have been shown
24 convincing data that it's efficacious. The issue
25 here is, is this worth the risk to patients for

1 this modest efficacy and having patients give
2 themselves shots every day with frequent injection
3 site reactions, risk of pneumonia, a risk of
4 cellulitis, and potential risk of leukopenia for an
5 efficacy equation that is really pretty modest.

6 I think that the difference here for
7 ACR20--first, before I sort of compare across
8 trials, I myself have had trouble with comparisons
9 across trials, so I think that is dangerous, but we
10 have consistency in these data that there is a 10
11 to 20 percent difference between the efficacy of
12 the anakinra and placebo, and that is a small
13 difference compared to leflunomide and
14 methotrexate, etanercept, all the other drugs that
15 either we standardly use or have recently been
16 released. The evidence here suggests this is less
17 efficacious, and we are dealing with a toxicity
18 that is perhaps as great as those.

19 So, I am frankly troubled by the
20 risk-benefit equation here, and I am not sure what
21 we should do.

22 DR. HARRIS: Dr. Wofsy.

23 DR. WOFSY: I think Davis has posed the
24 issue quite clearly, and it is challenging. The
25 data in a way speak for themselves very clearly.

1 There is almost going to be no argument about the
2 data, the presentations that we heard this morning
3 are consistent. Efficacy has been demonstrated
4 with a safety profile that at least at this stage
5 of the development looks like it is similar to a
6 lot of the other agents we use with some of the
7 same risks, but risks we accept and we monitor
8 carefully.

9 There is no doubt there are people out
10 there, 1 in 7, 1 in 10, who will be well served by
11 the availability of this agent. The question is
12 what about the risk to the other 9, and that is
13 what David has posed, but I mean the facts almost
14 couldn't be clearer.

15 DR. HARRIS: I will go with Dr. Elashoff
16 first and then Dr. Williams. We are all going to
17 comment, I am sure, on this question.

18 DR. ELASHOFF: What I want to do is
19 dissent a little bit from the statement that it is
20 really clear that efficacy has been proven, and I
21 have several comments to make on that. We have
22 only one study with 100 mg. Now, that does have a
23 small p value.

24 The other two studies, they don't have 100
25 mg, there are issues about adjustment for multiple

1 comparisons, and the two adjacent doses to 100 mg
2 don't show consistent significance in either case,
3 adjustment for multiple comparison, and the fact
4 that study 960180, the dose that looks significant
5 is the one that was started later and perhaps is
6 not entirely comparable to the placebo group.

7 I also want to bring up the issue of high
8 lost to follow-up, about 25 percent are lost to
9 follow-up. Now, this is true of other studies, for
10 other drugs, but in situations where we saw a
11 bigger drug effect.

12 In one study, 0560, the difference in the
13 way that missing data was dealt with made a 5
14 percent difference in the response rate. Now, 5
15 percent is kind of big when you are only talking
16 about 15 percent.

17 Lastly, there is the potential for bias
18 because of the injection site reactions. In the
19 placebo group, there was a difference of 11 percent
20 in the response rate between those who didn't have
21 an ISR and those who did with the higher response
22 rate in those who did, and that would have been
23 significant at about the 7 percent.

24 So, given the very small rate and all
25 these issues together, I think it has not been

1 demonstrated as clearly as one would wish that we
2 really can conclude that this is effective. There
3 is a lot of things that could make maybe a 5 or 10
4 percent difference floating around in here, and we
5 have only got a 15 percent difference.

6 DR. HARRIS: Dr. Williams.

7 DR. WILLIAMS: I actually agree with Dave
8 and Dave, that I think there is an efficacy
9 demonstrated, but it is relatively modest. Now, I
10 do think that if we look at ACR50 and ACR70, we are
11 talking about drugs like methotrexate and the
12 post-methotrexate drugs that really affect those
13 parameters.

14 I think that this drug has similar
15 efficacy to the pre-methotrexate drugs, and we
16 still use them in some patients. They are
17 individual patients. We have heard from two today,
18 Mr. Van Antwerp and the one that was read in, that
19 have had remarkable responses, and this drug I
20 think actually has a better safety profile than a
21 lot of drugs that we use as long as we are aware of
22 the concerns about infection.

23 So, I think that while it is modest in
24 efficacy, there is a role for it.

25 DR. HARRIS: Other comments? Dr. Brandt.

1 DR. BRANDT: Let me add a couple of points
2 to what has been said, a little different
3 perspective. It goes back to David Felson's point
4 from this morning about the ACR20 and the fact that
5 the lab results factor significantly into that,
6 because we heard in the clinical trial data that
7 there wasn't much of a change in swollen joints.

8 We heard then that there is not a
9 correlation between positive radiographic results
10 and clinical results. Well, that dichotomy, this
11 isn't the first time that dichotomy has occurred,
12 nor is this the only disease that occurs, but if
13 swollen joints is a reflection of synovitis, and
14 despite the positive impact of this on serologic
15 parameters, if it is not having much of an effect,
16 in fact, selectively poorer effect on that than on
17 other parameters that are being measured to which
18 there seems to be, lead to conclusions of efficacy,
19 I have got a little concern about that which
20 strikes me as a disconnect in terms of the biology.

21 DR. HARRIS: Dr. Callahan.

22 DR. CALLAHAN: Well, I am not a clinician,
23 but I agree with what Dave and David said about the
24 modestness of the impact, but the problem is, as
25 you point out, we did hear, as Jim pointed out, we

1 did hear from two people, and it is always that
2 issue that if people are given all the risks, and
3 then they can make a decision based on the risk and
4 what they wanted to do, but that is not always the
5 way it is marketed, but as David Wofsy pointed out,
6 there may be 1 in 10 people that it will have a
7 real strong impact on, and you just have to weigh
8 the risks for the other people and how that is
9 presented to the other people, and how the other
10 individuals are monitored, and if they are not
11 making an improvement, how it is monitored in that
12 fashion.

13 DR. HARRIS: Let me call on Ms. Malone. I
14 told you I would call you. Here you have an agent
15 that provides benefit, clearly benefit, a small
16 amount of benefit, there is some risk, maybe not
17 considerable, but there is risk.

18 As a patient, the question is what would
19 be your perspective in terms of is there a
20 sufficient benefit, to me, is there sufficient,
21 something I can get out of this relative risk, that
22 I might want to do this?

23 MS. MALONE: So much depends upon the
24 progression of your disease. There are patients
25 who may have tried so many drugs and finding them

1 not to work, they welcome anything, and so they
2 will tolerate far more risk than someone else
3 might, okay, who has not exhausted other therapies.

4 Of course, if you are one of these 17
5 percent, and you have phenomenal results, it is
6 wonderful, it is wonderful. So, it goes hand in
7 hand with education of the patient as to the risks
8 that are present, as well as education of the
9 doctor to be monitoring for these risks, but I
10 think just the idea of having something else
11 available just is very important and very hopeful.
12 That is what the patient is looking for.

13 You know, it is extremely frustrating with
14 some of the other medications when you find it is
15 not working. You hear all these wonderful stories,
16 and you think, well, why can't something work for
17 me, and if there is a chance that it can, I think
18 people will try it.

19 DR. HARRIS: Thank you.

20 Yes, Dr. Katona.

21 DR. KATONA: I would like to join the
22 group who is speaking up for this drug, because
23 working with patients, it is clear that we need
24 additional drugs to what we have, but maybe we
25 could better define the proposed indication.

1 When we are talking about failing one or
2 more disease modifying drugs, I am not sure that is
3 what we mean, failing, like these patients did not
4 really fail methotrexate, did not completely
5 respond to it, that is the reason we add another
6 drug to it, so somehow the message is not all that
7 clear.

8 The other thing in my mind we should
9 discuss, whether we should say that it can be used
10 alone or in combination, maybe we need to change
11 the order that it could be used in combination or
12 alone to encourage people that really use it for
13 the patients, 1 out of 10, as Dr. Wofsy mentioned.

14 So, I think it is an important drug, but
15 how the package insert is going to be written is
16 going to be very important.

17 MS. MALONE: I just have a question or
18 maybe something to propose, is that when in the
19 course of treatment would this be used, you know,
20 would you have to have failed methotrexate or maybe
21 have been on methotrexate for a while and have the
22 good results dissipate a little bit, I don't know.

23 DR. HARRIS: To my knowledge, a lot of
24 this is clinical judgment, but let me turn to the
25 FDA. Is there any sort of precedent for sort of

1 stating at what time in this armamentarium of
2 therapy, when does one actually use this agent?

3 DR. SCHWIETERMAN: The history is actually
4 rather clear. What the sponsor studies in the
5 clinical trial dictates the kind of indication that
6 the sponsor ultimately gets in the label.
7 Obviously, there can be some extrapolation from
8 that given that there are obviously very, very
9 rigid inclusion/exclusion criteria, and there has
10 to be clinical judgment as to whether that clinical
11 trial both shows efficacy in that population and
12 may show, in other words, there is some wiggle room
13 to expand upon that, but by and large, it is
14 entirely data driven, and then the Agency and the
15 sponsor work together with proposals to define
16 that.

17 The indication that the sponsor has
18 proposed here has been rather clear, for the
19 treatment of patients with moderately to severely
20 active rheumatoid arthritis in combination with
21 methotrexate therapy.

22 So, there is no specific, to answer your
23 question directly about whether there is the
24 ability to treatment patients who have failed other
25 kinds of therapies like anti-TNF therapies, there

1 simply are no data presented to the Agency with
2 regard to that, so to indicate it for that, unless
3 this committee feels otherwise, would not be
4 appropriate.

5 However, we have questions here about
6 whether these would be useful studies and the kinds
7 of studies that might be done, and would work with
8 the sponsor to design such studies in the future,
9 so that we could perhaps expand the indication.

10 One more important note, of course, is
11 that once the product is licensed according to a
12 particular indication, physicians are free,
13 according to the practice of medicine, to use it as
14 they see fit, obviously within the confines of
15 risk-benefit, so although the indication may not
16 call specifically for a particular kind of
17 subgroup, physicians, if they feel it is worth a
18 benefit to the patients, could do so.

19 DR. HARRIS: Dr. Abramson, did I see your
20 hand?

21 DR. ABRAMSON: Yes. I have nothing
22 profound to add, but just to comment that I share
23 the concern that the efficacy is not as great as we
24 would like to see. On the other hand, the
25 benchmarks of meeting an ACR20 response has been

1 met, and that is what is needed.

2 I think the issue that many people don't
3 respond to TNF blockers is a significant one, and
4 that the biological basis of this medicine would
5 lead one to think that there is a basis of its
6 mechanism of action is very important.

7 So, I think that my view would be to lean
8 towards favoring its introduction, recognizing that
9 the real impact of this medicine will be I think on
10 the structural changes, and if does indeed have
11 impact on structural progression, then, it will
12 find a very important place.

13 I think if it turns out that at one year,
14 the studies of x-rays are less robust than one
15 would like to see, it will be a much less important
16 medication.

17 I guess I am saying that I would like to
18 see the ACR--the ACR20 is a relatively low bar, but
19 in this context, the criteria were met, but I am
20 really looking forward to seeing what the
21 structural impact is going to be.

22 So, I think it is going to be a two-phase
23 kind of process to see where this agent really fits
24 in the treatment of the disease.

25 DR. HARRIS: Let me put something to you.

1 Suppose we don't have that structural data at this
2 time, but I think what the committee is trying to
3 deliberate and decide about is, is there sufficient
4 data without the structural studies to say, well,
5 there is sufficient efficacy to justify its use,
6 efficacy relative to safety.

7 DR. ABRAMSON: I think given the rules of
8 the game that we are engaged in, my answer would be
9 yes, that it has met the benchmarks of efficacy at
10 the criteria that we have set, and I wouldn't link
11 the approval to the structural changes.

12 My view is that the role of this drug over
13 time will depend more on that outcome than on the
14 more modest symptoms and signs impact.

15 MS. MALONE: Going through the data, I
16 didn't see anything relating to other liver or
17 renal problems or effects. Was anything done?

18 DR. BEKKER: Yes, we have indeed looked
19 very carefully at renal and liver parameters, and I
20 think I will answer your question shortly, and if
21 you need more detail, I can certainly go into that,
22 but we have looked at the renal toxicity profile in
23 detail, hepatotoxicity profile, and we did not find
24 evidence of an increased risk in patients taking
25 anakinra.

1 DR. HARRIS: Dr. Felson.

2 DR. FELSON: I guess I have a question for
3 the FDA at this point because a lot of the criteria
4 that have been put forward around the table for
5 whether this is acceptable or not are I guess what
6 I would characterize as absolute criteria, did they
7 show efficacy, is the safety profile acceptable.

8 I am wondering if it is time to move away
9 from that, and I don't know whether the FDA does
10 that or whether that is done in other diseases, for
11 other treatments, whether at a certain point you
12 say we have got a lot of treatments out there that
13 are more efficacious than this, with comparable
14 safety profiles, and it is likely that this isn't
15 going to add very much to the overall therapeutic
16 armamentarium in rheumatoid arthritis, where does
17 that factor in, and, yes, technically speaking,
18 they made all of the right statements. I mean it's
19 efficacious, its safety profile doesn't look like
20 it is all that dangerous.

21 DR. HARRIS: I could pose it differently.
22 How much efficacy is efficacious maybe?

23 DR. JAY SIEGEL: In most indications, the
24 standard for approval is that a drug be shown to be
25 efficacious. In some, there is cut points as to

1 how much it needs to be, to be clinically
2 meaningful. In some sense, the use of the 20 in
3 the Agency, 20 is that on an individual patient
4 basis.

5 Then, the amount of efficacy that is
6 needed is, in most indications that come before the
7 Agency, compared to the safety profiles. So we are
8 looking for a relative assessment of benefit versus
9 risk, and not generally in most indications--and I
10 will give the exception in a moment--compared to
11 the efficacy of alternative medications.

12 So, you come out with a new treatment for
13 skin rashes or headache pain, blood pressure, don't
14 necessarily have to be even as good, if you are
15 effective, and often there is a reason, because of
16 tolerance or responsiveness or whatever, that some
17 people might benefit from that diversity of
18 therapy.

19 In some settings, and this is most
20 commonly in settings where efficacy has been
21 measured in terms of effects on mortality or
22 significant and irreversible morbidity, we do
23 require effectiveness at a level that approaches or
24 is as good or better than approved drug, so
25 thrombolytics for acute myocardial infarction,

1 cancer agents, if they are simply effective, but
2 have no clear place in the armamentarium, often
3 cancer agents have some role in people refractory
4 to everything else, even if they are not as good as
5 alternative therapies.

6 So, it is complex and nuanced questions.
7 In most indications, though, we look at the drug,
8 its efficacy versus its safety, not its efficacy
9 versus sometimes a preset standard, not usually,
10 and not usually versus other products.

11 I mentioned a presumption that drugs might
12 be useful in people that don't tolerate or don't
13 respond to other agents, and you all, of course,
14 have talked about the potential that this drug will
15 offer value in patients who have failed other
16 treatments that you perceive to have higher
17 response rates.

18 I would simply note, as I think Dr.
19 Schwieterman alluded to, we don't have data
20 regarding that question. Some sponsors choose to
21 develop a drug that way, to study people who have
22 failed a specific drug. Often, when you look at
23 those people, the response rates in populations
24 selected by failure of drugs, particularly if
25 mechanisms are related or not, may be different,

1 and in some cases, lower than response rates in de
2 novo-treated populations.

3 So, I wouldn't necessarily presume that
4 what you see in a de novo treated or in people who
5 have failed perhaps two or three standard DMARDs
6 will be the same response rate that you might see
7 in people who failed some newer drugs. That is
8 just a question we don't have an answer to yet, but
9 we will be speaking about, I think, in a bit.

10 DR. WOFSY: I also have a question in
11 large part for the FDA to help clarify my own
12 thinking about this. Roughly a year and a half
13 ago, it sounds like you had some information on
14 this, and you discussed with the sponsor what else
15 they would need to show, and included studies in
16 children, which initiated and included this large
17 safety study that is now completed.

18 It also included an x-ray study that isn't
19 completed, and, in part, I am wondering if that is
20 what you needed to have this discussion, why are we
21 having it without the one, your x-ray data.

22 DR. JAY SIEGEL: I don't think we ever
23 indicated, and we have not indicated to any of our
24 sponsors, that you need your x-ray data for an
25 indication regarding effect of the signs and

1 symptoms of rheumatoid arthritis.

2 You need that once you have a signs and
3 symptoms claim, to supplement it with a claim
4 regarding effects and x-ray progression. So, the
5 x-ray data were presented here, there are six-month
6 data, there is data missing, whatever, the company
7 thought they were important, and we think they are
8 important, too, in part because they are less
9 susceptible to bias by injection site reaction
10 effects, for example, and so they are indications
11 potentially, if you accept them as suggestive of an
12 effect, they are indications of a drug activity
13 although not we would think supportive by our
14 normal standards of a claim for an effect on
15 radiographic changes and structural changes.

16 But that said, we recommended that study,
17 but not as a necessity for part of a package for a
18 signs and symptoms claim.

19 DR. WOFSY: Can I just follow up on that
20 just to describe without intent to draw conclusions
21 the dilemma that I am sitting here facing, which
22 is, of course, not one that is anticipated
23 prospectively, and that is, if given some of the
24 issues that Dr. Elashoff raises, for example, if I
25 were sitting here with x-ray data that showed no

1 statistically significant benefit at the end of a
2 year, and no statistically significant benefit in
3 swollen joints, I would be more leery and more
4 concerned about the potential biasing of the
5 injection site reactions.

6 On the other hand, if I was sitting here
7 with what I suspect will be the case, based on the
8 six-month data, with a pretty convincing impact on
9 x-ray, then, I would be less inclined to be
10 concerned about the issues that were raised with
11 regard to the injection site reactions, more
12 inclined to be confident and comfortable about the
13 efficacy data.

14 So, it turns out although one might have
15 had no way to see it prospectively, that the sort
16 of dilemma I am sitting here with the level of
17 response we are seeing is really looking for some
18 other hard objective piece of evidence, which that
19 could provide.

20 DR. SCHWIETERMAN: Let me just add to Dr.
21 Siegel's comments. In our response to Amgen last
22 year, we did not specify that there needed to be a
23 12-month radiographic study or a six-month clinical
24 signs and symptoms study, we just simply said that
25 the data as presented to us were inadequate to

1 support the safety and efficacy, and agreed to the
2 proposal made by Amgen, much as we agree to lots of
3 proposals by sponsors with clinical trial designs
4 to consider results through the six-month clinical
5 time point, thinking what Dr. Siegel said, that in
6 general, we don't require 12-month radiographic
7 data to get a signs and symptoms claim, and with
8 the idea that it was possible and that with the
9 six-month signs and symptoms data, that this
10 committee would find the data adequate.

11 I have no issues with the ideas that you
12 put forward, that if we were to have those
13 radiographic data, it would be perhaps a much more
14 compelling picture, but the question we were
15 presented with, was this a possible solution to the
16 problem that they had, the answer was yes.

17 DR. ABRAMSON: If I could just follow up
18 on that, because I think David makes a point at
19 least in a going forward way that is very useful.

20 To treat the signs and symptoms of
21 arthritis in the post-methotrexate area, we really
22 should think going forward about NSAID-like drugs,
23 which may be ACR20 not comparable to this, and
24 DMARD drugs, where we now infer that there is going
25 to be radiographic, slowing of radiographic

1 progression, so at least as time goes on, we tend
2 to think we use a DMARD and there is good evidence
3 that will slow the x-rays. Hopefully, that will be
4 the case here, too, but we don't have those data.

5 The cost-benefit or the safety-efficacy
6 ratio that we, as an advising group, would accept
7 for an NSAID-type drug versus a structural modifier
8 DMARD-type drug are very different, so I think some
9 of the dilemma that you see in these comments is
10 precisely what David was expressing, is that this
11 kind of drug, which has a safety profile akin to
12 DMARDs, now is the whole package or probable
13 structure modification going forward.

14 It doesn't mean that retroactively, you
15 should hold people to different standards than we
16 have, but this committee, I think needs to think
17 about DMARDs' safety profile and what the sponsor
18 really wants to get ultimately as an approval, not
19 just signs and symptoms, if that is ultimately not
20 going to be the major approval that they are
21 seeking.

22 DR. HARRIS: Steve, I may go a little
23 further with that because, of course, we have
24 debated this about a year or so ago with respect to
25 the importance of structural data, how long to

1 study it for, and so on.

2 Do you grant, though, that there may be a
3 number of instances in which there may be a
4 separation even with DMARDs between structural
5 response and an actual symptomatic response, and
6 quality of life response?

7 DR. ABRAMSON: Absolutely. I think the
8 mechanisms of pain, inflammation, and structural
9 damage are going to be different, and it won't be
10 surprising to find some agents that are better at
11 the structure. I think that is whether it's
12 doxycycline or some other medicine, we may see.

13 I think that is to be expected. It may be
14 that is where this agent may appear, it may be less
15 inflammatory events, and more structural things, I
16 don't know.

17 So, I think thinking about them separately
18 is important. The issue that we have always
19 debated is whether you can get structural change
20 without signs and symptoms. This agent, for
21 example, gives you signs and symptoms, not as
22 strong perhaps as some of the other DMARDs in the
23 other classes, but there is no reason to think it
24 won't get structural changes based on different
25 mechanisms of action.

1 The question is can the safety profile,
2 you will accept more toxicity if you are affecting
3 disease progression than if you are only affecting
4 signs and symptoms.

5 DR. HARRIS: I am going to call for a vote
6 on this. Ms. Malone, would you like to make
7 another comment before I call for a vote? I want
8 to be sure that this is discussed completely and we
9 have heard each other's views, and then I want to
10 vote.

11 MS. MALONE: I just wondered when we will
12 have the radiographic results, when will we know if
13 it does retard structural damage. Anybody?

14 MS. BEAR: The x-ray data in 145 should be
15 available about mid-year, next year.

16 MS. MALONE: So, that is like a year from
17 now.

18 DR. JAY SIEGEL: That is when you would be
19 ready to submit it or that is when you would have
20 the data in house?

21 MS. BEAR: The data will be ready for
22 analysis sometime Q2 next year.

23 MS. MALONE: What kind of time frame will
24 we have the results, like when did you start taking
25 the x-rays, et cetera, gathering the data? What

1 time period are we talking about for the patients?

2 DR. PERLMUTTER: I am not sure I
3 understand the question precisely.

4 MS. MALONE: How long will these patients
5 have been followed?

6 DR. PERLMUTTER: This is a one-year study.

7 MS. MALONE: Okay, it will just be the one
8 year.

9 DR. PERLMUTTER: This is the one-year
10 study. We will have a complete data set, we hope,
11 in the middle of next year, and there is a
12 substantial data analysis phase, of course, and
13 that information would be submitted along with the
14 additional information that we have accrued to this
15 point.

16 MS. MALONE: And is this the one where the
17 25 percent were missing?

18 DR. PERLMUTTER: No, no, no, that is a
19 different issue.

20 MS. MALONE: So, you should have complete
21 numbers.

22 DR. PERLMUTTER: Every study, it is
23 impossible to gather 100 percent data on every
24 study. Technically, it is impossible.

25 MS. MALONE: Right, but hopefully, there

1 would be less lost than 25 percent.

2 DR. PERLMUTTER: There will be some
3 missing data, we can't speak to what the level of
4 that will be, because inevitably, there are some
5 problems with compliance in different sites and
6 multiple investigators. These are very complicated
7 to address.

8 DR. HARRIS: Let me read what we are going
9 to vote on. Really, I will modify the bolded part
10 of this question. Given the overall benefit, which
11 is modest, and a potential increased risk of
12 serious infection, do these data demonstrate an
13 appropriate safety and efficacy profile of the
14 agent anakinra as a treatment for rheumatoid
15 arthritis? Do these data demonstrate appropriate
16 safety and efficacy profile as a treatment for
17 rheumatoid arthritis?

18 DR. JAY SIEGEL: Might I ask just as
19 clarity, on the white version, there were the words
20 "for approval as a treatment for rheumatoid
21 arthritis," and just to make clear that is what we
22 are asking, because I think that would be the most
23 useful thing for the vote to specifically address.

24 DR. HARRIS: For approval. So, let me
25 just be sure about that, just being a little

1 compulsive about that.

2 Do these data demonstrate an appropriate
3 safety and efficacy profile of anakinra for
4 approval as a treatment for rheumatoid arthritis?

5 Now, for each person voting, I am going to
6 ask that you give your name prior to your vote and
7 a short comment if you want to, you don't have to,
8 and we will start with Dr. Katona.

9 DR. KATONA: My name is Ildy Katona.
10 Being a pediatric rheumatologist, this is not
11 something that I really feel comfortable since I
12 have not seen any data on children. So, if it is
13 at all possible, I would like to abstain.

14 DR. HARRIS: Noted.

15 Dr. Felson.

16 DR. FELSON: I am struggling with this a
17 lot. I guess my answer is going to be no. I think
18 notwithstanding the FDA's concerns and suggestions
19 about following the rules, I think the efficacy
20 here is so very modest and the safety issues are
21 substantial, and I guess given that overall
22 balance, I would vote against.

23 DR. HARRIS: Ms. Malone. Remember to give
24 your name.

25 MS. MALONE: Leona Malone. As a patient,

1 I am anxious for anything to come out that is going
2 to offer some help and some solution, if not
3 solution, some amelioration. I am not familiar
4 with clinical data enough to really cast a vote in
5 the same type of league with you people, but it
6 does fulfill the requirements that FDA set up.

7 So, I would say a very quiet yes.

8 DR. HARRIS: That is why you are here.

9 Thank you.

10 DR. WILLIAMS: I would say yes. I think
11 that it has met the demonstration of efficacy. I
12 don't think it will replace methotrexate or some of
13 the later drugs, but I think it will help some
14 people, and I don't think its safety profile is any
15 worse and probably a little better than many of the
16 drugs we are currently using.

17 DR. ANDERSON: Jennifer Anderson. Those
18 two little words "for approval" are very important.
19 With those words in there, I would vote yes, but
20 with them taken out, I would vote no, because the
21 data are adequate, it seems, for approval given the
22 way the guidelines for these things are written by
23 the FDA, but I have reservations about whether, you
24 know, if you take out those words, do the data
25 demonstrate an appropriate safety and efficacy

1 profile as a treatment, I don't think that has been
2 shown yet, but that is not what we are voting on.

3 DR. JAY SIEGEL: Wait a second. The law
4 requires that a drug be safe and effective for
5 approval, and there seems to be a lot of confusion
6 about these guidelines and what they mean, because
7 there have been three comments that this meets the
8 standards for approval, but we are not sure about
9 whether it actually is good.

10 I am not sure, I don't like that
11 distinction at all. The guideline, which first of
12 all is a guideline, okay, so it's a guideline and
13 has to be viewed that way, it is not law, the
14 guideline is a standard for what it takes to show
15 efficacy, and it speaks to an effect on the ACR20,
16 and this agent has had trials with outcomes on the
17 ACR20 as per the guideline for the appropriate
18 duration or whatever to assess that question of
19 ACR, effect on ACR20.

20 If the questions the committee are
21 struggling with are is this benefit good enough
22 to--and there are guidelines about how many
23 patients to study in an efficacy, in a safety, but
24 there is no guideline about how safe is safe--so if
25 the question you are struggling with is, is the

1 efficacy good enough to warrant the safety, there
2 is no guideline on that. There is nowhere where we
3 say if you have a 10 percent effect on ACR20, and a
4 2 percent or whatever you think, whatever it is,
5 serious infection, that that is or does or does not
6 meet a standard, there is no guideline.

7 So, as to the question of whether the
8 benefit warrants the risk or the other question as
9 to how certain the benefit is, as some of you have
10 raised based on other issues, those are not
11 addressed by a guideline.

12 So, I would ask you not to divorce the
13 issue and say, well, this met some rule and
14 therefore has to be approved. The question before
15 you is does it have an appropriate safety and
16 efficacy profile for approval. That means by law,
17 is it safe and is it effective, and by
18 long-standing tradition, is it safe means is it
19 safe in light of the benefits that accrue. A
20 cancer drug has a profile that would be considered
21 totally unsafe for a headache pill, so safety is in
22 the context of efficacy.

23 So, is it safe and effective to meet the
24 legal standard for approval means does it have an
25 efficacy and safety profile that are such. In

1 other words, the question we are asking is
2 not--there isn't a guidance that sets a strict
3 level, it is rather asking for an integrated look
4 as to whether this ought to be deemed a safe and
5 effective drug for use on the marketplace.

6 DR. HARRIS: I think we got it.

7 [Laughter.]

8 DR. HARRIS: But since this is such
9 important business, and we have gone quite a way,
10 half around the room, but I think this is extremely
11 important, does anybody feel any differently based
12 on what was said?

13 MS. MALONE: Maybe I should make my yes a
14 little more robust.

15 DR. HARRIS: Dr. Anderson?

16 DR. ANDERSON: I know it is very
17 difficult, probably impossible to determine
18 risk-benefit exactly, and the trade-off question is
19 very much a matter of judgment, an individual
20 judgment, so I don't know that this will ever be
21 resolved.

22 Certainly, you know, there are a lot of
23 drugs that get--well, I don't know how much they
24 are as a percentage of drugs approved--but
25 eventually, the safety turns out to not be--you

1 know, there are other things come up about safety,
2 so I still would say what I said before, that yes
3 for approval, but don't know yet for the real
4 answer as distinct from a legislative answer.

5 DR. JAY SIEGEL: I just want to make sure
6 that I am firmly on record as stating that a
7 recommendation that a drug is safe and effective
8 enough for approval, but we don't yet know if it's
9 safe and effective is not a recommendation that I
10 am comfortable working with because it suggests a
11 misunderstanding of the legal question.

12 DR. HARRIS: You could abstain.

13 DR. JAY SIEGEL: I don't mean to be,
14 really, I don't want to be rude about this, but I
15 don't want any public perception that the--the
16 legal standard is safe and effective, in fact, as
17 judged, if you read through the legal standard by
18 experts, and to say, well, an expert opinion is I
19 am not sure if it's safe and effective, but it
20 should be approved, it is almost a contradiction of
21 our law. It leaves me troubled.

22 DR. ANDERSON: I think I had better change
23 my vote to no. Thank you.

24 DR. HARRIS: Let me just comment that this
25 is part of the struggle that everybody is facing

1 really right now, and I wonder sometimes how the
2 question is posed, you know, sets up precisely this
3 sort of uncertainty.

4 My view is that rheumatoid arthritis is a
5 chronic disease. I think invariably for treating
6 physicians, very few patients stay on the same
7 DMARD for long enough or can stay on the same DMARD
8 for long enough, and invariably, over a period of
9 time, we are going to have to choose among several
10 agents because of the nature of the disease and the
11 fact that none of these agents really are able to
12 provide the sort of benefit to patients over long
13 enough period of time.

14 So, given that, I feel that although the
15 benefit of this agent is modest, without a doubt
16 it's efficacious and it provides some benefit, and
17 as far as its safety, although there are safety
18 concerns, I don't feel given the nature of the
19 other agents available, given the fact that we
20 worry about safety concerns, given what the data is
21 here, I feel not alarmed enough to think that the
22 safety would detract from the efficacy that one
23 gets out of it.

24 I think this may be a beneficial agent. I
25 think in the scheme of things where a treating

1 physician may well have to utilize many agents at
2 different times, we are going to invariably meet a
3 subset of patients, even if it's a third of
4 patients, such as the ones that we saw today, who
5 may derive some benefit, and, as such, I think
6 without a doubt, I will vote yes. I am Nigel
7 Harris.

8 DR. BRANDT: Ken Brandt. We certainly
9 haven't solved all of the therapeutic problems with
10 rheumatoid arthritis, and this isn't going to solve
11 the therapeutic problems with rheumatoid arthritis,
12 but I think that it does offer an option.

13 I think that basically, it is what you
14 just said, Nigel, and looking at the safety and
15 efficacy data, there are some things that we don't
16 have that only time will give us, but taking all of
17 this into account, I would vote in favor.

18 DR. CALLAHAN: Leigh Callahan. I agree
19 with what Nigel and Ken Brandt said. I think when
20 you have a disease where most people have the
21 disease sometimes 20 to 30 years, you go through
22 most of the drugs that are available, and, yes,
23 this is not the magic bullet, and it is a very
24 modest effect, but I think based on what the
25 clinicians have said, that the safety issues are

1 not out of range of the current drugs that are
2 being used, and so I would vote yes.

3 DR. WOFYSY: David Wofsy. I have the good
4 fortune I think in sitting in this place at the
5 table, unlike the other people who have voted, to
6 know that it is 5 to 2 at this point, and my vote
7 won't swing the balance.

8 [Laughter.]

9 DR. WOFYSY: Damn good thing, too. I will
10 address the issue directly, but I do want to start
11 by saying I had tried to get the Chair's attention
12 when we started around for the vote, and the reason
13 for that is, as I will explain in a moment, that I
14 would prefer to vote on this after all of the
15 discussion of this afternoon because I think some
16 of the things we haven't discussed yet are
17 pertinent to this issue. I will try to explain
18 that, but also address the question you have asked
19 us at this point.

20 To be explicit on the points that were the
21 subject of contention a moment ago, I think that
22 there has been a demonstration of efficacy, not
23 beyond a shadow of a doubt, but pretty convincing.

24 I think there has been a demonstration of
25 an acceptable safety profile. No drug is perfectly

1 safe. This drug isn't perfectly safe. For one,
2 would not be inclined to exaggerate the problems
3 that were encountered in this trial. There were
4 some adverse effects of this agent, and I think
5 they are manageable.

6 So, I can answer those questions which
7 really are at the heart of this vote, but here is
8 the dilemma. For the FDA, I think, for the public,
9 and for the sponsor, this, as has been pointed out,
10 is sort of a binary question. Go away with
11 approval or without approval, the opportunity to
12 use this drug or without the opportunity to use
13 this drug.

14 My dilemma is that I am having trouble
15 thinking about it as a binary question for the
16 following reason - because although I have just
17 said that the data presented to us demonstrate at a
18 level that is acceptable to me, efficacy and
19 safety, my concern is that through no fault of the
20 sponsor, the way that science proceeds, the
21 population in which this drug has been studied, and
22 the population from which we have drawn that
23 information, may well not be the main population of
24 people who take this drug.

25 That casts some doubt in my mind on the

1 safety part of the answer. I think given the
2 concerns about the relatively modest effect, it is
3 likely that people will try other agents before
4 this agent, and will proceed, having failed, say, a
5 TNF inhibitor as an example, that many of the first
6 generation of patients who take this will be in
7 that category.

8 It will therefore either be added to other
9 agents with the potential for toxicity or it will
10 be used in people who, as it has been pointed out,
11 may be less likely to respond because they are more
12 refractory patients.

13 So, that, frankly, is my level of concern
14 and why I think the rest of the discussion this
15 afternoon is at the heart of what I am worried
16 about, because once the binary decision is made
17 here, the rest of us who don't make binary
18 decisions, who make a different decision for this
19 patient than for that patient and for the other
20 patient, are going to be operating in an existence
21 where the questions that come up about the use of
22 this agent are not going to be addressed by the
23 data that was presented here.

24 That is what is at the heart of my
25 uneasiness with a yes/no answer on this question.

1 If you want a yes/no answer on this question to my
2 satisfaction, safe and efficacious.

3 DR. HARRIS: Well, thank you so much for
4 your comment. I presume I will be correct in
5 saying we are advisory.

6 DR. WOFSY: I just want to amend the end
7 of my comment. This is David Wofsy again. Safe
8 and efficacious in the population studied.

9 DR. HARRIS: Of course, we are advisory
10 for what that means.

11 There were?

12 MS. REEDY: That were 6 yes, 2 no, and 1
13 abstain.

14 DR. HARRIS: Thank you.

15 DR. JAY SIEGEL: I would point out we also
16 have a tie vote in that Dr. Felson has indicated
17 that this should have been the first question, and
18 Dr. Wofsy indicated it should have been the last
19 question.

20 [Laughter.]

21 DR. HARRIS: We will let the FDA deal with
22 that. Thank you.

23 The next question. David, I am going to
24 ask you actually to start, once we start commenting
25 on this, because I think some of this expands on

1 some of what you say, and an opportunity to
2 revisit.

3 Used in combination with other
4 immunomodulatory agents, it is likely that anakinra
5 will sometimes be used in combination with other
6 therapeutic agents, including anti-TNF agents.

7 Safety data for the combination of anakinra with
8 etanercept are very limited. Data from one small
9 open-label study showed a relatively high rate of
10 patient withdrawal from the study (21 of 58) and
11 serious adverse events (7 of 59), including four
12 serious infections.

13 Please discuss these safety data.

14 The specific question, No. 5: Were
15 anakinra to be licensed, what types of
16 contraindications, warnings, precautions or
17 guidance should be given in the package insert
18 regarding the use of anakinra with other
19 immunomodulatory therapies, especially anti-TNF
20 agents?

21 So, it is a broader question than the
22 anti-TNF agents, but I think here comes the
23 opportunity to make some additional recommendations
24 with respect to the parameters with which this
25 agent might be prescribed.

1 David.

2 DR. WOFSY: Well, I have sort of partially
3 commented on my concerns in this area. I do think
4 this will be an important area for this drug. The
5 community has been primed by a whole variety of
6 basic science that has come out around this, some
7 of which was presented today, and by some buzz
8 about this to anticipate using this agent in
9 combination.

10 I mean it has been two years, you talk
11 within the rheumatology community, and people are
12 thinking of combinations, and I think that, as I
13 pointed out before, that impetus will be given
14 added pressure by the fact that the data show that
15 alone, this isn't so strikingly beneficial, so
16 people will be thinking, what combination should I
17 use it in.

18 It may or may not be marketed in precisely
19 that way, and we have no information really on its
20 benefits in that situation, and a little
21 information that is somewhat worrisome with respect
22 to toxicity, this 12 percent serious adverse event
23 number.

24 Now, some of those serious adverse events,
25 if I am recalling correctly, are an electrocution,

1 so I want to make it clear that I understand that
2 this 12 percent of serious adverse events is
3 certainly an overestimate in that population of the
4 serious adverse events that were related to this
5 drug. One was a barbiturate withdrawal. So, it
6 may be lower than 12 percent.

7 On the other hand, as you point out, there
8 are other agents it might be combined with. We
9 have no knowledge of that. So, I do think this is
10 at the core of my concern. At some level, we have
11 to try to make, as I did in response to your last
12 question, try to stand back and make sort of an
13 unprejudiced statement about our analysis of the
14 data, and at some point, we have to sort of put on
15 our rheumatologist hat and say how is it going to
16 be used and how comfortable am I with that.

17 I think this is going to be a major area
18 of its use, and we don't have any information, and
19 that is worrisome.

20 DR. HARRIS: Let me just ask you one other
21 question. We have, in fact, seen some data about
22 some combinations here, but do you think that the
23 anti-TNF agents, based on the very limited data we
24 have, does that rise to a significance based on
25 some of the potential adverse effects here above

1 the rest, and then what does one do about that?

2 DR. WOFSY: I am not sure I understand the
3 question, so let me restate my understanding of it.
4 How concerned am I about this small pilot study of
5 58 people with something somewhat less than 12
6 percent serious adverse events over a six-month
7 period?

8 It doesn't look to me--how shall I put
9 this--I think those data provide a very limited
10 basis for making a judgment. They certainly are
11 not a strong source of worry, and that is why I
12 point it out, that the serious adverse events
13 include an electrocution and other things that are
14 clearly not related to the drug.

15 On the other hand, because of the way in
16 which that study was designed, all we can get from
17 it is a sense that there may have been more, a
18 higher frequency of serious adverse events than in
19 the larger safety studies that were done, and we
20 have no insight into efficacy, the uncontrolled
21 graphs on ACR20, and such, look like placebo graphs
22 or they look like study patients, I mean in the
23 absence of a control group, and I am sure the
24 sponsors made it clear that they weren't trying to
25 draw more information from it than that, and

1 certainly we can't.

2 So, I think there is not much there to go
3 on, so what I am trying to express, I think in too
4 wordy a fashion, is that my concern is from our
5 ignorance. It is not because the data that was
6 presented to us causes great source of worry. It
7 is because we don't know.

8 DR. HARRIS: Dr. Felson.

9 DR. FELSON: I guess for the first time
10 today I disagree with Dr. Wofsy. I think there is
11 58 people treated and 4 of them developed serious
12 infections, which are well enumerated on therapy.
13 Now, that is a rate of 7 percent. That is higher
14 than the rate that was seen when etanercept was
15 here for approval.

16 One would not have accepted a 7 percent
17 serious infection rate with etanercept alone, I
18 think, versus placebo. Now, that is versus
19 placebo, and the problem here, I think you raised
20 it earlier, and I agree with it, is that we don't
21 necessarily know in these types of patients, 58 who
22 were studied, what the expected rate on etanercept
23 of serious infections would have been, or whether
24 those serious infections were somehow precipitated
25 by the addition of anakinra.

1 I think the minimal data we have, and I
2 don't disagree that there is not a lot, is
3 worrisome, and I think I am concerned about the
4 safety in that population of adding anakinra to
5 etanercept notwithstanding the biological
6 rationale.

7 I am especially concerned because of the
8 biological rationale and because that combination
9 will be encouraged, and now that we have a little
10 preliminary data that suggests the combination is
11 dangerous and could kill people, okay, let's be
12 blunt about it, this is not something we want to
13 do.

14 I think what it warrants is I would
15 suggest a labeling that it not be used with
16 TNF-alpha inhibitors until there is better data
17 that suggests it is comparably safe when given in
18 combination to TNF-alpha inhibitors given alone.

19 That is what you were suggesting earlier
20 when you asked for control data, I think, David,
21 you know, and it requires a clinical trial in which
22 patients on etanercept are randomized to either
23 anakinra addition or placebo.

24 One could design a trial. All of the
25 methotrexate trials that are done widely, including

1 their own methotrexate trial, which is partial
2 responders, and unfortunately, we now know there
3 are a lot of partial responders to etanercept and
4 infliximab.

5 Maybe that is the right design here, but I
6 see this preliminary data, and frankly, I am
7 scared, and I think especially with an agent where
8 the data does not suggest tremendous efficacy, I am
9 not really crazy about giving approval to put
10 patients at risk of what might be life-threatening
11 infections. That is hard to buy.

12 DR. JAY SIEGEL: Just a comment about
13 this. I think nobody could disagree that there
14 aren't a lot of data, and it is hard to know with
15 minimal data how concerned to be. I would like to
16 point out I think you have given the numbers right
17 in that 7 percent, the lower end of the confidence
18 interval is around 1.9 percent, which suggests that
19 it is a range unlikely to have seen with rates that
20 we saw with monotherapy.

21 The other thing I would remind you, that
22 Jeff pointed out, is that there were two patients
23 with leukopenia down to 1,000 out of that 58. I
24 think we didn't see that at all in the hundreds of
25 patients treated with monotherapy, and both of

1 those patients had infections.

2 I guess the other thing I think that went
3 into the picture, as Dr. Perlmutter pointed out,
4 for joint pathology, that these agents have some
5 very similar effects. There are many processes
6 mediated by both.

7 That is the reason for the hope that use
8 of them together would be helpful, but it is true
9 on many of the tissues in the body, that they have
10 related effects in the inflammatory process, so it
11 stands as also at least a significant theoretical
12 concern that just as they may work together, they
13 might work together in helping out beneficial
14 effects, they might also work together in helping
15 out some unwanted effects, we just don't know.

16 You expressed your feelings about how it
17 would be used and your concerns, but didn't
18 specifically address the question about what you
19 thought we ought to do in labeling, and labeling
20 presumably will have some impact, maybe less than
21 some of us might want to think on how the drug is
22 used, but I wonder, do you have thoughts or
23 recommendations as to how we should address these
24 issues in labeling?

25 DR. WOFYSY: Well, I do think they are

1 inherent in the comments. David and I have a
2 different way of phrasing some of these things, but
3 I am not sure we disagree that much in the sense
4 that you said initially, as well, that without the
5 controlled trial, we don't know, and that is why I
6 emphasize that this is an area of ignorance and
7 concern, however you put it on.

8 An argument can be made, frankly, that a
9 population of TNF-treated patients who are doing
10 sufficiently poorly that they might sign up for a
11 trial to go on yet another unknown agent, might be
12 a particularly sick population of rheumatoids who
13 would be more likely to have bad things happen to
14 them.

15 I am not arguing that that is what
16 happened. I am just saying we don't know. So, I
17 don't think there is a big difference, but we see
18 these data that concern us. For me, I sort of term
19 it in terms of my ignorance and concerning, you
20 term it in terms of those four people concerning
21 you, I view as very differently, but I think with
22 respect to the question you have posed, I would
23 think it would be important to discourage people
24 from using this combination and to encourage people
25 to do the study that will answer these questions.

1 DR. HARRIS: I am going to ask Dr.
2 Williams in a minute, but let me just ask both of
3 you again, when you say discourage, you mean
4 discourage it all together or a big, bold warning,
5 providing it is licensed, on the label?

6 DR. FELSON: I think the FDA would need to
7 suggest options there, but I am not sure. I mean I
8 am not sure what the options are. I think anything
9 from the use of this agent in combination with
10 TNF-alpha inhibitors should be discouraged at the
11 current time as there is no evidence that this
12 combination--or there is evidence that this
13 combination may not be safe for patients, or a
14 warning, I don't know exactly what the options are.

15 DR. JAY SIEGEL: The options range from
16 contraindication through boxed warning, bolded
17 warning, warning, any of which, of course, there is
18 many options in terms of what the wording is, and
19 for all of which there are standards and
20 regulation, and there are precedents, and it is a
21 very complex picture.

22 I think most helpful for us would be what
23 is the message, should it be absolutely not used
24 under any circumstances, should it be strongly
25 discouraged, but with room for people to judge, and

1 we can apply I think the appropriate labeling
2 working with the company based on that, because to
3 go through--I don't have before me the regs for a
4 contraindication, for example, and all the
5 precedents, and it would be hard to ask this
6 committee I think to vote to specify those issues.

7 DR. HARRIS: Dr. Williams.

8 DR. WILLIAMS: Much of what I had to say
9 has been said, but I am not quite as pessimistic as
10 Dr. Felson. I think we do have data to suggest
11 that anakinra is safe with methotrexate. I think
12 there does need to be some sort of warning with TNF
13 inhibitors, and I would probably state it as that
14 with small numbers of uncontrolled data, there
15 appears to be increased infection in the
16 combination, because I agree with Dr. Wofsy, this
17 drug is going to be used, not as monotherapy, but
18 as additive therapy, and they ought to be aware
19 that if they add it to TNF inhibitors, they might
20 increase the risk of serious infection.

21 DR. HARRIS: Let me start by posing this
22 question, not so much for a vote, does anybody have
23 a concern, a really significant concern that there
24 needs to be a warning with respect to a combination
25 of this agent with any of the non-anti-TNF agents,

1 which would be things like methotrexate,
2 hydroxychloroquine, Imuran, and so on, based on the
3 data?

4 DR. WILLIAMS: The only data you have is
5 with methotrexate. I don't think you can expand
6 that to anything else. I think the only thing you
7 have is data with methotrexate.

8 DR. BEKKER: Maybe I could just comment.
9 In the large safety study, we have included other
10 disease-modifying agents. Leflunomide was added
11 and other DMARDs.

12 DR. WILLIAMS: That's right, I forget
13 about that study, and in that regard, no, I
14 wouldn't have concern.

15 DR. HARRIS: Of course, I hate to say so,
16 but we don't have a breakdown, and, you know, how
17 much of each was used, but we certainly know about
18 methotrexate, so certainly with respect to
19 methotrexate, presumably, there is no concern in
20 terms of that combination.

21 Let's go to the anti-TNF agents. I think
22 clearly there is a concern. The issue is does the
23 concern rise to the level of a contraindication,
24 anybody feels at the table that, in fact, they are
25 concerned enough that this combination--of course,

1 the data is very limited, and we don't know, but I
2 think do we, even with this limited data, are we
3 concerned enough to say that this combination, this
4 particular combination should be contraindicated?

5 DR. WOFSY: No, I would not say it should
6 be contraindicated. If this drug is approved, it
7 is not at all difficult to imagine a human being
8 suffering with rheumatoid arthritis on another
9 agent, who makes an informed decision to take this
10 risk.

11 DR. FELSON: As usual, I agree with Dr.
12 Wofsy, no, I think there should be a
13 contraindication. I think 7 percent serious
14 infection rate in a small sample is too high, and I
15 think what we might consider doing is suggesting
16 there be a contraindication that could be removed
17 at such time when there is data from a controlled
18 trial that suggests that that risk of infection is
19 not as concerning as the preliminary data suggests
20 it is.

21 I think that at this point, given these
22 data of 4 serious infections in 58 people, that is
23 a concerning risk, and I would be inclined to sort
24 of suggest that there be some kind of warning.

25 DR. HARRIS: Of course, David, how are we

1 going to do that if, in fact, there is a
2 contraindication, how do you convince patients to
3 use this combination if it is contraindicated, I
4 mean how do we get the other data?

5 DR. FELSON: Actually, it isn't patients
6 or doctors that are going to do that, Nigel, I
7 think it is going to be third-party payers are
8 going to do that.

9 DR. WILLIAMS: I think if there is a
10 contraindication, that legally, I would be worried
11 about trying to use that combination, because I
12 think there is a risk of infection, and I have no
13 protection if there is a contraindication, one of
14 the reasons I wouldn't put it in--

15 DR. HARRIS: I missed the end there.

16 DR. WILLIAMS: For that reason, I wouldn't
17 list it as a contraindication, I would tell them
18 about the risks.

19 DR. HARRIS: I think I get a sense that
20 most people around--I am sorry, Dr. Brandt, I
21 should have eyes behind my head.

22 DR. BRANDT: I would go along with David.
23 I think that the data are not adequate, but I think
24 this is serious business, and I would rather err on
25 the side of safety given all that we know about

1 this, and when and if data appear from appropriate
2 trials to show that this was ultra-conservatism,
3 great, but in the meantime, seeing what we saw
4 here, I would be very nervous especially when you
5 consider how this will be used in the community.

6 DR. HARRIS: Well, given that, I am
7 wondering if we shouldn't go around the table on
8 the issue of contraindication, because I think it
9 is important that we understand that in terms of
10 giving at least our guidance with respect to
11 recommendations.

12 Dr. Katona.

13 DR. KATONA: I would go with the
14 contraindication especially I have to think about
15 children. That is important.

16 DR. FELSON: I think I said my piece.

17 MS. MALONE: I agree with Dr. Felson, but
18 I think the contraindication should be able to be
19 removed once they do a study or find out.

20 DR. WILLIAMS: I have already stated I
21 would not make a contraindication.

22 DR. ANDERSON: Assuming the drug is
23 licensed, I guess I agree with Dr. Williams that
24 you won't be able to do the studies if there is a
25 contraindication, if that is really true that legal

1 problems would prevent them, so I would suggest
2 something other than a blanket contraindication on
3 the label.

4 DR. HARRIS: For my own mind, I would
5 issue whatever is the strongest warning below
6 contraindication simply because I think, I wish
7 that we could get more data. Now, obviously, does
8 one say, you know, do you put people at potential
9 risk knowingly, so that you can decide whether or
10 not it should be contraindicated, but I think that
11 there are enough questions out there, I think with
12 a strong enough, the strongest possible warning
13 short of contraindication. So, contraindication,
14 no.

15 Dr. Brandt.

16 DR. BRANDT: I would favor
17 contraindication until we have better data.

18 DR. HARRIS: Dr. Callahan.

19 DR. CALLAHAN: Contraindication until we
20 have better data.

21 DR. WOFSY: I think I am still on record
22 with Dr. Harris. I need data for the
23 contraindication just as much as I need data for
24 the indication, not quite as much for the reasons
25 that people have said, but I would stick with the

1 strong warning.

2 DR. HARRIS: I would call this a split
3 vote regardless of whatever numbers we have here,
4 so I am going to leave it in the hands of the FDA.
5 Thank you.

6 Let's go to No. 6. Were anakinra to be
7 licensed, what types of additional studies should
8 the sponsor conduct to better characterize the
9 safety and efficacy of anakinra when used with
10 other immunomodulatory therapies, especially
11 anti-TNF?

12 This addresses studies that one might do.
13 Anybody who wants to start? Dr. Wofsy again maybe?
14 No, no, you don't want to, okay.

15 Let's start with Dr. Williams, why not.

16 DR. WILLIAMS: Well, actually, I am just
17 going to suggest the one that Dave Felson has
18 already suggested, that is, that you take patients
19 who are inadequate responders to etanercept, and
20 add to them in a double-blind fashion anakinra, and
21 to do a double-blind, controlled trial on partial
22 responders to etanercept with or without anakinra.

23 DR. HARRIS: Dr. Felson.

24 DR. FELSON: I guess I would try to make
25 that both an efficacy and safety trial, because it

1 sounds like there was nice preliminary data here
2 that was quite uncontrolled, that suggested a
3 little bit of efficacy, and it would be nice to see
4 whether that combination that seems so biologically
5 plausible actually is correct in vivo, and also
6 make it large enough that you can detect the kinds
7 of safety concerns that we were talking about.

8 Actually, I am not sure it has to be that
9 huge, because the safety concerns in this 58
10 patients were so obvious that it doesn't suggest
11 that you need thousands of patients.

12 DR. HARRIS: Dr. Williams.

13 DR. WILLIAMS: However, for efficacy, you
14 are going to need fair numbers, if you are only
15 going to 16 or 17 percent to the efficacy.

16 DR. HARRIS: Dr. Brandt, would you enter
17 patients in such a trial?

18 DR. BRANDT: Sure.

19 DR. HARRIS: Quick answer.

20 Do you think you have gotten enough?

21 DR. SCHWIETERMAN: I just want to make one
22 important point. We have talked about the
23 etanercept data, but there are other agents out
24 there, as well. Does the committee have feelings
25 in general about infliximab and Arava? I know they

1 have been mentioned before, but would these
2 inclusion criteria be specific for one therapy or
3 broad?

4 DR. HARRIS: Comments?

5 DR. ABRAMSON: I think we shouldn't
6 frankly be too restrictive at all, either limiting
7 to the study design that was just proposed or to
8 the drugs. I think once this drug were to be
9 licensed, any number of possibilities should be
10 studied including not just failures on TNF
11 blockers, but perhaps a combination of both of
12 these agents, you know, TNF blocker and this agent
13 versus other drugs like methotrexate.

14 I think there should be no a priori
15 restrictions to the kind of clinical trials that
16 should be done, that might be mechanism-based or
17 based on the biology.

18 DR. HARRIS: Dr. Williams.

19 DR. WILLIAMS: You can't necessarily get
20 combination studies with every combination, and
21 they did have the one large study with multiple
22 agents, so the one I really have most concern about
23 is the small, open-label with etanercept, and I
24 just don't think we know anything about safety or
25 efficacy. I don't accept efficacy on an open-label

1 study, and safety, there were some concerns raised.

2 So, if I were going to prioritize, I would
3 do that one absolutely first, and then I think you
4 can look at all of them to show that there are
5 advantages, I think actually leflunomide would be a
6 good one to look at. You have already got one with
7 methotrexate, and once you have covered TNF
8 inhibitors, leflunomide, and methotrexate, you have
9 got most of the current big drugs.

10 DR. HARRIS: If I could comment, too, that
11 I think we should prioritize in terms of looking
12 particularly for safety with respect to this
13 particular combination, because I think that is
14 where there is a lot of concern.

15 Any other comments? Okay.

16 DR. JAY SIEGEL: Let me just ask
17 something. Our concern in terms of premarketing
18 commitment, it is largely going to be focused on
19 addressing the safety concerns here, and your last
20 comment mentioned the safety concern, but there are
21 the questions you raised earlier, and I am just
22 from a scientific perspective interested in the
23 sense of the committee that there are a lot of
24 unanswered questions about effectiveness in
25 refractory populations or whether combinations will

1 be more effective than monotherapy.

2 I wonder if there is other comment about
3 that and whether, if there is going to be a safety
4 study for combination therapy, whether efficacy
5 ought to be worked into that, as well.

6 DR. FELSON: This harkens back to
7 something David said earlier, which I thought was a
8 very important comment, that a lot of them are
9 long-standing rheumatoid arthritis patients with
10 more disability, high HAQ scores, and more tender
11 joint counts, but they are not of older patients,
12 and many, many of our patients are older now.

13 I think the other piece that is missing
14 here is the piece that David was commenting on,
15 which is sort of in those patients, and there are
16 some comorbidities in the safety trial, but not as
17 many as we often see, especially in our older
18 patients often who have rheumatoid arthritis.

19 I mean why not encourage a trial here of
20 patients who really are more like the typical
21 community-based rheumatoid arthritis patients, who
22 tend to be older, tend to have other diseases, and
23 let's get a sense, because we are dealing with an
24 efficacy-toxicity trade-off that is sort of on the
25 marginal side, and to get a sense of whether the

1 toxicity then is beyond that we might get out of
2 efficacy, I think may be of interest, and it would
3 tell us something that is going to be pretty
4 clinically useful.

5 DR. HARRIS: David.

6 DR. WOFSY: I think I will ask for a small
7 clarification of that, David. I certainly agree
8 with you that that is an important question, and we
9 can think of other important questions, but I also
10 find myself sitting here recognizing the practical
11 obstacles of really addressing that kind of
12 question.

13 It is one thing to sort of comment on it
14 from the perspective of the table, but enrolling
15 people in these trials is already problematic in
16 the climate that involves if you are trying to
17 enroll across all age groups against other agents
18 that are enrolling, against patients who have
19 access to new medications.

20 I would love to see the answer to that
21 study, and I didn't push the microphone button to
22 disagree with the importance of that information in
23 any way, but I must say I found myself sitting here
24 saying, boy, that is going to be one tough task to
25 undertake, maybe even not possible.

1 I don't know how to deal with that kind of
2 an issue. It certainly would be a very big
3 challenge to get an answer to this question.

4 DR. FELSON: I agree with you. I think
5 given the efficacy-safety trade-offs here, that
6 particular population is an especially important
7 one to study. It may not be so important in the
8 other therapies we have available to us.

9 In some of the cardiovascular studies,
10 they do this. I mean they limit to or recruit lots
11 of subjects in specific age categories. Some of
12 the TIMI studies have done it up to age 85. There
13 aren't very many people even in the safety
14 comorbidity study that are over age 75.

15 The mean age of patients with rheumatoid
16 arthritis now is in the early 60s. The mean age of
17 their safety data is 56, and they have 25 percent
18 of their subjects are 65 and over. A very large
19 percentage of our RA patients are 65 and over.
20 Especially given the issues with this particular
21 therapy, I think it would be very valuable to know
22 that.

23 DR. HARRIS: I think we would agree,
24 though, that the safety data is the most important
25 to get after first. If one were designing that,

1 perhaps one then wants to look at this other
2 population, particular populations which may have
3 particular comorbidities, the ones that we treat,
4 but safety first.

5 Now, let me push on. Should anakinra be
6 specifically studied in the setting of patients who
7 have failed a TNF blocking agent?

8 DR. WILLIAMS: You have to define failed,
9 and I define that as inadequate response, and that
10 would be the same study we have already suggested.

11 DR. HARRIS: Any other comments? David.

12 DR. WOFSY: The point has been made before
13 that as more and more agents come on the market,
14 there will be more and more combinations of studies
15 that you could imagine, things together, things
16 after failure, things additive with success. They
17 can't all be done.

18 I think the study that has been proposed
19 is the important one. It will shed some light on
20 some of this, but I wouldn't ask for another one.

21 DR. HARRIS: FDA, is this the answer that
22 you are comfortable with, or were you trying to get
23 more out of this?

24 DR. SCHWIETERMAN: We were simply trying
25 in this question to reflect some of the concerns

1 raised earlier in the morning about I think what
2 Dr. Wofsy stated, and perhaps others, about
3 different subpopulations that would likely be
4 affected by this, and wanted to be sure that all
5 our questions covered the concerns that were
6 raised.

7 This question really is about anticipating
8 off-label use and anticipating the safety and
9 efficacy of off-label use given some of the
10 concerns we have about the modest risk-benefit
11 ratio here.

12 So, just for my own clarification, there
13 is a difference between--I am not exactly sure what
14 kind of study we would do in the anti-TNF failures.
15 I guess Dr. Williams raised it there. There are a
16 number of patients who have no response to anti-TNF
17 therapies whatsoever, and I guess my question is
18 should this be studied in those, as well.

19 DR. WILLIAMS: When we look at these, I
20 would lump those with the inadequate responders,
21 otherwise, you are looking at two separate studies,
22 which can be quite costly. I think there are not a
23 lot of TNF total failures. I think if you have
24 those and you want to study them separately and see
25 if anakinra will benefit them when TNF did not, or

1 TNF inhibitors did not, you are looking again at
2 monotherapy, or would you be adding it to them?

3 If you are adding it to them, then, you
4 look at those patients who have inadequately
5 responded, and an inadequate response is also
6 failure.

7 DR. HARRIS: It doesn't sound as if we are
8 generating much more discussion here, so unless
9 there is anything else.

10 DR. JAY SIEGEL: I may have missed
11 something. The question here differed from the
12 previous one. That was more focused on studying
13 the combination, and I think this one was more
14 focused on whether monotherapy should be studied in
15 the setting of anti-TNF failures.

16 It was your response that you just don't
17 think there is enough total anti-TNF failures to
18 make that an important question to address?

19 DR. WILLIAMS: I think you are going to
20 have to get a lot of centers to get enough patients
21 to look at, and I am not sure that I find that as
22 important as those who are inadequate responders.

23 DR. JAY SIEGEL: In which case you would
24 be more interested in looking at an add-on or
25 perhaps--well, given the safety issues, you might

1 want to look at both.

2 DR. WILLIAMS: I would consider you can
3 make them the same study. Inadequate response
4 would also be failure, and so you would just have
5 all patients who didn't have an adequate response
6 down to no response at all, and add anakinra to
7 that group.

8 DR. JAY SIEGEL: Again, do you think it
9 would be a more interesting study to add anakinra
10 rather than to replace in that group?

11 DR. WILLIAMS: Based on what I have seen,
12 I don't expect anakinra to replace TNF inhibitors.

13 DR. BRANDT: It is really two separate
14 questions and studies for two different purposes.

15 DR. JAY SIEGEL: Right, and that is why I
16 wanted to be clear, because I understood that there
17 was interest in the add-on therapy, and I was
18 trying to find out the extent to which you thought
19 that looking at it as a replacement for people who
20 had inadequate response was worth looking at or a
21 high priority to look at or not.

22 You might say I guess, as you have said,
23 that based on the lower response rate, it might not
24 be, on the other hand, you could have different
25 pathophysiological mechanisms where some people

1 might respond better to one or the other.

2 DR. WILLIAMS: You don't know unless you
3 look, and so if you have that specific question, I
4 think it is going to be a harder study to do.

5 DR. BRANDT: But that is an efficacy issue
6 in a special population of a compound which has
7 modest efficacy in other populations. The other
8 question is a burning question, and that is the
9 safety of combination therapy.

10 DR. HARRIS: The last question. Please
11 comment on the proposed development plan of
12 anakinra for use in pediatric patients with JRA
13 including the proposed randomized withdrawal study
14 design as a means to establish a use in patients
15 with JRA.

16 I am going to ask Dr. Katona to start, and
17 then Dr. Elashoff, I am going to ask you next, I
18 plan to.

19 DR. KATONA: I have a long list of
20 questions that I would like to clear up, but just
21 really concentrating very first on the study
22 design, this study would use an open-label phase
23 for 12 weeks, and then randomize the responders for
24 an additional 16 weeks to placebo or anakinra.

25 Now, my major question, and that is

1 probably to the sponsors, do we have any
2 information. So far we know who responded, how
3 long the response last, will they flare, the ones
4 who responded, and can we qualify that response as
5 a response? It is very difficult to know the
6 biology as well as the clinical manifestations.

7 DR. BEKKER: Unfortunately, it is too
8 early to comment on this study. We have enrolled
9 34 patients so far, and we have really done very
10 little in terms of any analysis.

11 DR. KATONA: Have you completed any parts
12 of the first 12 weeks?

13 DR. BEKKER: I do not know exactly what
14 number of patients have completed at this time.

15 DR. KATONA: Just continuing this, it
16 probably bothers me a little bit less because a lot
17 of times in pediatrics, we use drugs which have
18 shown efficacy in dogs, and the two things which we
19 are very particularly interested in children, one
20 is safety, the other one is PK studies.

21 Have you done any of those?

22 DR. BEKKER: In terms of the safety,
23 obviously, in the study, the safety profile is
24 being monitored on an ongoing basis, and really, so
25 far, we have seen there was one case of varicella

1 infection. This patient recovered fully.

2 There was one withdrawal due to injection
3 site reaction, and that was really the significance
4 of what we have seen so far.

5 In terms of pharmacokinetics, the study
6 also has incorporated in it a population,
7 pharmacokinetic component, so to collect samples on
8 patients throughout the study.

9 DR. KATONA: Are you using different
10 dosage regimens, do you go up like to 2 mg/kg?

11 DR. BEKKER: No. The study is designed,
12 as I pointed out, for patients to receive 1
13 mg/kg/day up to a maximum of 100 mg.

14 DR. KATONA: What is the cutoff, what is
15 the youngest patient in this study?

16 DR. BEKKER: In terms of the inclusion
17 criteria, I think we are going down to four years.

18 DR. KATONA: That is under four, I think
19 we wrestled with the very same question with
20 Enbrel, the first time we cut it at four, and I
21 would like to ask the FDA, what you eventually do
22 with the population under age four.

23 DR. JEFFREY SIEGEL: I think generally,
24 the approach we have done in the past is to enroll
25 the older children into the randomized trials, but

1 then to ask the sponsors to collect information in
2 a registry fashion on children age two to four.

3 DR. BEKKER: I am sorry, I just want to
4 correct. Actually, two is the lower limit.

5 DR. KATONA: What about, this study is
6 enrolling positive and negative polyarticular
7 patients, are you taking the rheumatoid factor
8 positive just like they would be adult patients?

9 DR. BEKKER: Let me just bring up this
10 slide. This represents the key eligibility
11 criteria for the study, two to 17 years of age,
12 greater or equal to 10 kg with active polyarticular
13 course JRA greater or equal to 5 swollen joints,
14 greater or equal to three joints with limited
15 motion, greater or equal to four-week washout of
16 other biologic agents, no significant medical
17 condition affecting the safety or efficacy
18 assessment.

19 If given methotrexate, it is the only
20 permitted DMARD in the study, should be given at a
21 dose between 10 and 40 mg/square meter/week, and
22 then the NSAID and the corticosteroid doses should
23 be stably maintained for four weeks prior to study
24 and during the study.

25 So, we do have specifically rheumatoid

1 factor eligibility criteria.

2 DR. KATONA: That probably means that you
3 include both groups. What about, do you have any
4 special precautions for giving immunizations to
5 children until they are on anakinra?

6 DR. BEKKER: I am sorry. Could you repeat
7 the question?

8 DR. KATONA: Do you have any guidelines
9 that these children should be immunized, receive
10 any type of immunizations, or shouldn't receive
11 live viral immunizations or anything, is that part
12 of the protocol?

13 DR. BEKKER: We do have a requirement that
14 they be immunized prior to entering into the study
15 and during the study.

16 DR. KATONA: That is not what I mean, like
17 any of the routine immunizations, can they receive
18 until they are in the study or you call those up,
19 these usually come up in the general pediatric
20 visit, and one needs to think about it and include
21 it in the protocol.

22 DR. BEKKER: We do not withhold any
23 immunizations.

24 DR. HARRIS: Do you think that is
25 important, Dr. Katona?

1 DR. KATONA: I probably would address it
2 because there is just a lot of confusion about that
3 issue, especially anytime when children are treated
4 with any biologicals, one does not want to give
5 them either to them or to the siblings any live
6 virus vaccine.

7 I think that you might want to just go
8 back. It is a very simple thing to add to the
9 protocol.

10 DR. HARRIS: Are you finished, Dr. Katona?

11 DR. KATONA: I think I exhausted my
12 questions, yes.

13 DR. HARRIS: Dr. Williams.

14 DR. WILLIAMS: I just have a question for
15 Dr. Katona. Are withdrawal studies commonly done
16 in pediatrics? I was wondering why we went to a
17 withdrawal study instead of a straight efficacy
18 study.

19 DR. KATONA: The reason in pediatrics we
20 have to go to the withdrawal study, because we
21 cannot use any double-blind studies. It is
22 considered not ethical to do the double-blind study
23 in children, so that is the reason they are
24 designed this way, so I think this is the second
25 best or like the best what one can do in

1 pediatrics, and it is far from perfect, so that is
2 the reason.

3 By and large, the entire pediatric
4 community wants kinetics and the safety, we just
5 use the drugs that rheumatologists are using. We
6 like to see the studies, but sometimes we do not
7 get the 100 percent answer, and I don't know whether
8 this sums it up.

9 DR. SCHWIETERMAN: That does sum it up,
10 but I want to make it clear that randomized
11 withdrawal studies are not the only option that the
12 Agency discusses with sponsors, nor is it the only
13 kind of treatment design that some sponsors elect
14 to pursue even in pediatric JRA studies.

15 I just think for the record, I need to
16 make clear that there are other options that have
17 been employed with these things, and I think that
18 it is still a debate in the community as to when to
19 do it and when not to.

20 DR. HARRIS: Dr. Elashoff.

21 DR. ELASHOFF: My concern is with the
22 design of this study as it is done, because it
23 seems to me that it exposes a maximum of children
24 to the anakinra on a basis in which we can't infer
25 much of anything about safety because we have no

1 comparison group, and then the after-the-fact
2 randomized part looks to me like it is going to
3 have extremely low power either for safety or for
4 efficacy.

5 So, from a statistical point of view, you
6 are maximizing the safety risk and sort of
7 minimizing both the efficacy and the safety
8 information that you are getting from this kind of
9 trial.

10 So, I would certainly from a statistical
11 point of view, be opposed to this type of trial.

12 DR. HARRIS: I really would like a comment
13 because in my own mind, I had some questions
14 certainly at to the design.

15 DR. SCHWIETERMAN: This is a complicated
16 question because we routinely ask sponsors to do
17 the best trial that provides the most information
18 for the patients, and almost always that design in
19 adults is the randomized, controlled study, such as
20 the one they did here.

21 In the pediatric community, however, as I
22 mentioned in my earlier response, we also recommend
23 these kinds of designs to sponsors, but they are
24 not always ones that are easily or readily accepted
25 by the community, depending upon the investigator's

1 perceptions.

2 So, during the course of our conversations
3 with these various sponsors, we have debates about
4 the kinds of things that Dr. Elashoff just pointed
5 out, about whether this is, in fact, an optimal
6 design overall for risk and benefits, and so forth,
7 but we, just to get to the point, have limited say
8 in what the investigators are willing to do and
9 what they are willing to go forward with.

10 So, I think what the field really needs is
11 an open debate about how to pursue these kinds of
12 trials in the pediatric population given that there
13 is a diversity of opinion as to how you can do it
14 and how you can ethically do it.

15 It is an open question, and I think the
16 points that everyone is raising are good ones, that
17 not only are there some limitations to the study,
18 but you can even envision that there might be
19 reasons not to do it this way, but on the other
20 hand, it is very difficult in this setting.

21 Just to point out the other point of view,
22 since we don't have a lot of pediatric
23 rheumatologists here, to randomize your child to a
24 placebo arm when there is some perception of
25 benefit, just to cut to the quick there.

1 DR. KATONA: There is one other practical
2 point which we, in the pediatric community, we are
3 facing. Anytime we try to put through a protocol,
4 our Human Use Committees, most of the committees
5 look at it, whether it has an individual potential
6 benefit for the participant, and they are much
7 tougher to approve anything that is much harder in
8 the pediatric community, so that is one of the
9 reasons, by and large, the pediatric community
10 tends to go this way.

11 But I think Dr. Elashoff's comment from
12 the second part of the study is something that
13 maybe could be considered, and if there would be
14 higher numbers in the second part of the study,
15 maybe the study would have much more power, and
16 that should not be difficult to generate. There
17 are plenty of these patients out there.

18 DR. HARRIS: There is a comment from our
19 sponsor, and then I will ask Dr. Anderson.

20 MS. BEAR: Yes. Let me just comment that
21 the power for the second part of the study is 90
22 percent for a delta of 0.4 with the current sample
23 size.

24 DR. ELASHOFF: That is a lot bigger delta
25 than you saw in adults, almost three times.

1 MS. BEAR: Well, we are hoping that--these
2 are disease flare rates--and we are hoping that we
3 will be able to see this effect.

4 DR. BEKKER: Yes, you are looking at it
5 differently. This is disease flare rate in the
6 placebo group versus anakinra, and so we
7 anticipate, you know, the guess is 0.6 versus 0.2
8 in terms of the flare rate, so it is a different
9 way of looking at the data.

10 DR. ELASHOFF: But it is definitely pretty
11 low powered for safety.

12 DR. ANDERSON: My question has to do with
13 flare, just how it is defined, and also what the
14 sponsor knows about flare in the adults that they
15 have studied, who have come off the drug.

16 DR. BEKKER: Essentially, patients would
17 be looked at in terms of their JRA, at the JRA
18 study core set components. If I could have slide
19 ASZ17.

20 [Slide.]

21 These are the JRA core set components that
22 would be looked at in the study. These are
23 different if you are used to the adult criteria.
24 They are slightly different, but similar to a large
25 extent, subject pain, number of active joints,

1 tender/painful joint counts, swollen joint counts,
2 and limitation of motion.

3 DR. ANDERSON: But how is flare defined
4 and also do you have any information on flare,
5 however you might define it, among adults that you
6 have studied?

7 DR. BEKKER: I am not quite clear what
8 your question is.

9 DR. ANDERSON: You have values of all of
10 these parameters at the beginning of a time period
11 and at the end, and you must be defining flare in
12 terms of some combination, some function of the
13 changes during the time period, and also how does
14 this relate to flare in adults that you have
15 studied?

16 DR. COHEN: The question is in the
17 pediatric population to define the flare. What
18 criteria, meaning the flare, in that study.

19 DR. BEKKER: In the double-blind period,
20 in the open-label part of the study, the JRA core
21 set criteria are being used to say whether a
22 patient responds or not, and if they respond, then,
23 they would enter the double-blind period. If they
24 flare during that study, and I am not exactly sure
25 what the criteria for that is, but if they flare,

1 they would then be counted in the nonresponder
2 category.

3 We can get that information for you, I
4 just don't have it with me.

5 DR. COHEN: As far as adults, all the
6 patients that we have studied in the United States
7 have been on methotrexate. When we looked at
8 efficacy, the 757 was a safety study with multiple
9 DMARDs.

10 When patients go off the drug, who are
11 responding, they do poorly. It is not like
12 stopping methotrexate was. We don't see the
13 terrible flare, but we do not have criteria for
14 that, because the studies were not designed to look
15 at that, but very quickly after going off of
16 therapy, the patients get worse.

17 DR. HARRIS: Dr. Katona.

18 DR. KATONA: I think that just answered my
19 question, because my question was whether there are
20 any plans, four months is not enough for the
21 children to flare, whether the study would be
22 extended, but I think we could expect them to flare
23 if they do rather quickly.

24 DR. HARRIS: We may be sitting here in
25 another several months commenting about the

1 approval of this agent in the pediatric patient
2 population, and I am wondering, in fact, some of
3 the very people may be around the table, and I am
4 wondering, Dr. Katona, Dr. Elashoff, Dr. Anderson,
5 whether or not there are specific things that one
6 might suggest with respect to the study design.

7 Of course, the horse is out of the stable,
8 but the question is whether or not there are things
9 here that bother you, that may affect what happens
10 later on.

11 Dr. Katona?

12 DR. KATONA: I think the easy one was the
13 immunization. That could be very easily added. It
14 wouldn't be any problem. I personally would have
15 liked a 1.0 and a 2 mg just because, in general, in
16 children, per kilo, we have to use more drugs like
17 methotrexate, the average dose we are using is
18 between 0.6 to 1 mg/kg. They have much better
19 metabolism. I would have preferred, but I am not
20 sure that could be added to the protocol anymore.

21 DR. HARRIS: Of course, risk may increase.

22 Dr. Elashoff.

23 DR. ELASHOFF: There will be, well, you
24 actually don't know how many will be randomized.
25 They are estimating, I guess, on the basis of how

1 many they think will be responding, although the
2 estimate is about 68. So, you are expecting about
3 34 in a group.

4 So, you essentially can't even estimate
5 any rates lower than about 3 percent. I mean you
6 either see zero or 1, and 1 is a 3 percent rate.

7 So, I don't see it as providing, unless
8 there is something scary in the first 200 patients,
9 I don't see it as providing any real reassurance
10 about safety, a study like that.

11 DR. JAY SIEGEL: I guess that is based on
12 the presumption that the critical need for safety
13 data in children is from controlled trials. There
14 is a lot of adverse events, unlike 70-year-olds,
15 maybe children with JRA are substantially different
16 in this regard, but there are a lot of adverse
17 events that children don't experience, and if you
18 see them on a drug, the need for a controlled group
19 may be less.

20 I guess maybe I could ask Dr. Katona that
21 question. If in the open label part of this, so
22 there is 68 children, and if we see some serious
23 infections or other serious infections or other
24 serious complications, is the background rate of,
25 say, serious infection or other complications in

1 children with JRA sufficiently high that in a
2 six-month or a 12-week period of 68 children--

3 DR. ELASHOFF: It is 200 open label, 68
4 expected to go on.

5 DR. JAY SIEGEL: Right, who would be
6 responders and then be randomized, or could we just
7 assume, just look at the serious adverse events in
8 an unlabeled way?

9 DR. KATONA: This is a hard question. In
10 general, in children with polyarticular JRA, the
11 infection rates are really not higher even on the
12 ones who are on methotrexate. Enbrel is a
13 different story. That is the reason I would be
14 very careful about this.

15 I don't think that we are going to get the
16 final answer from this many children. It is
17 something very important. Then, eventually, we
18 will set down what we went through with the warning
19 label, what we are going to provide for the adults,
20 a similar warning is going to be put in for
21 children until we get some postmarketing data. It
22 usually takes a long time to really get the real
23 picture.

24 But the same way for the adults, it was
25 expressed very eloquently that you need the drugs.

1 We had the same way with children, they are just
2 not enough drugs out there, so we really would like
3 this to come into our arena, as well.

4 DR. HARRIS: Dr. Anderson.

5 DR. ANDERSON: I have a couple of
6 questions about the blinded phase of the study. Is
7 it going to be double-blinded? Also, are there
8 going to be more frequent evaluations than just at
9 the beginning of that and the 16 weeks, and if so,
10 will patients be determined to have flared the very
11 first time that they do flare, and then that is the
12 end of the study for them, or do they stay in their
13 group without being taken out until the end of the
14 16 weeks?

15 DR. BEKKER: There is a number of
16 questions there. The first question, in terms of
17 double-blind, yes, the second part of that study
18 will be completely double-blind.

19 In terms of the schedule of study
20 procedures, in the second part, patients would be
21 evaluated every four weeks during that phase, so
22 they would be assessed on that basis of whether
23 they flared or not, and if they flared, obviously,
24 they would exit the study, would go into a two-week
25 follow-up period.

1 DR. HARRIS: Are there any other comments?

2 DR. FELSON: My recollection of the
3 therapeutic armamentarium of pediatric rheumatology
4 is that it is littered prior to methotrexate with a
5 lot of trials and drugs which never showed efficacy
6 in part because of underpowering. I guess this
7 therapy doesn't have a big effect to start with,
8 and I think the notion that they are going to have
9 34 in each group and be able to show an effect is
10 concerning.

11 I think that the sponsor might need to
12 consider getting more subjects in order to see if
13 this fits into that therapeutic armamentarium. I am
14 not sure this is enough. I don't know whether
15 there is data that you get more sensitivity out of
16 a flare design, withdrawal flare design.

17 DR. JAY SIEGEL: Randomized withdrawal
18 studies under certain assumptions of biological
19 effect, which is at its short term and it ends
20 after therapy, are actually--

21 DR. FELSON: More efficient.

22 DR. JAY SIEGEL: --efficient, so that
23 these 68, just studying the 68 responders, all of
24 whom you know are responders, and eliminating from
25 the pool the 132 nonresponders, can under certain

1 assumptions be more efficient whether done as a
2 withdrawal, but it can be more efficient than
3 withdrawing everybody, or it doesn't make much
4 sense to withdraw a nonresponder, or even then de
5 novo randomization of a couple hundred patients
6 because you are going to have those 132 in there
7 who, whichever arm you give them, are going to blur
8 out an effect, whereas, these 68 responders, some
9 of them are placebo responders, but many of them
10 are not, should be more powerful.

11 But that said, there is a lot of
12 assumptions in there. It depends on the proportion
13 that are placebo responders, but it also depends on
14 mechanism of action of a drug, and frankly, it is
15 not clear to me, even though the drug is gone after
16 a day or two, whether after 12 weeks of this
17 therapy, the effect on the disease might well
18 persist for months thereafter, and the flares may
19 not come until too late, so it is very hard to
20 predict, I would say, until we get the data, until
21 we see what it says.

22 Of course, if it's underpowered, that
23 doesn't mean, or if it doesn't show an effect, that
24 doesn't mean necessarily it's the end of the
25 question. You assume that it doesn't work, and

1 might be the step toward figuring out another way
2 to look at the question, either through a larger
3 study of the same design or a different design.

4 DR. KATONA: Usually, the pediatric
5 studies are designed to show an ACR30 instead of
6 20. Is this the same? You usually get an ACR30
7 for pediatric response. Is this the same? It is
8 going to be very interesting to see whether there
9 will be responders or not in the pediatric
10 population, if it is the same.

11 DR. BEKKER: I am sorry. Could you just
12 repeat the question?

13 DR. KATONA: For JRA, the usual study
14 designs look for 30 percent improvement versus 20
15 in the adults, your ACR20. Is this same for
16 anakinra?

17 DR. BEKKER: Yes, we use the same.

18 DR. HARRIS: Do you feel as if you have
19 gotten enough out of this?

20 DR. SCHWIETERMAN: Yes, thank you.

21 DR. HARRIS: I think that brings us to the
22 end of our questions, Ms. Reedy?

23 MS. REEDY: I want to remind the committee
24 that we meet in closed session at 8:00, and to tell
25 the public that the public sessions begins at 10:00

1 tomorrow.

2 DR. HARRIS: I will adjourn the session.

3 Thank you.

4 [The proceedings were recessed until 8:00

5 a.m., August 17, 2001.]

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